CLINICAL STUDY OF THE COMPARATIVE EFFECTS OF CAPTOPRIL AND DIGOXIN IN CONGESTIVE HEART FAILURE

THESIS

FOR

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C E R T I F I C A T E

This is to certify that the work entitled "CLINICAL STUDY OF THE COMPARATIVE EFFECTS OF CAPTOPRIL AND DIGOXIN IN CONGESTIVE HEART FAILURE " has been carried out by DR.SANJAY LAKHTAKIA himself in the department of Medicine.

He has put in the necessary stay in the department of Medicine as per University regulations.

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C E R T I F I C A T E

This is to certify that the work entitled "CLINICAL STUDY OF THE COMPARATIVE EFFECTS OF CAPTOPRIL AND DIGOXIN IN CONGESTIVE HEART FAILURE", which is being submitted as a thesis for M.D.(Medicine) examination of Bundelkhand University, 1990, has been carried out by DR.SANJAY LAKHTAKIA under my direct supervision and guidance in the department of Medicine. The techniques employed in the thesis were undertaken by the candidate himself and the observations recorded have been periodically checked and verified by me.

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T O M Y P A R E N T S

A C K N O W L E D G E M E N T S

Indebt

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C O N T E N T S

INTRODUCTION

INTRODUCTION

On the most fundamental level,heart failure represents the failure of the heart to supply adequate blood, and hence nutrients and oxygen,for the metabolic needs of the various tissues of the body.

Since its introduction by William Withering in 1785,digitalis,along with diuretics has been the mainstay of therapy for congestive heart failure(CHF)for over two centuries. Recent studies have,however,demonstrated that digoxin could be discontinued in patients with stable heart failure and sinus rhythm without any long term adverse effects.It has also been shown that long term digoxin therapy may be clinically beneficial only in patients with heart failure accompanied by atrial fibrillation,and when the failure has persisted despite diuretic treatment.Besides,digitalis is a toxic drug with a low therapeautic-toxic ratio.The effects of digitalis therapy on the survival of patients with ischemic heart disease and its proarrhythmic effects have become a focus of concern. Whether the benefits of digoxin therapy in CHF outweigh its risks has become debatable.As such,the role of digoxin,in cases of heart failure,has fallen into controversy.It is also well known that digoxin and diuretics may not always suffice for cases of severe heart failure,and for acute forward failure.

On the other hand,the role of afterload in

determining cardiac performance,neglected for quite long,has recieved attention in the recent years.Vasodilator therapy was introduced into the management of CHF about two decades ago.It has now become a standard therapeautic approach for the treatment of CHF,more so when it has become refractory to the conventional mode of therapy employing the inotropic agent digitalis to augment the cardiac output,and the diuretics for preload reduction and relieving pulmonary congestion.Arteriolar dilators improve forward flow by reduction of systemic vascular resistance,i.e.,afterload,thus increasing the stroke volume and cardiac output with their beneficial effects to follow. The venodilators reduce the preload,thus augmenting the cardiac output and relieving pulmonary congestion.

CHF is attended by a number of neurohumoral changes that probably evolved as counteractive mechanisms to maintain perfusion in response to a reduced blood flow,and that are responsible for both the excessive preload and afterload in CHF.There is increase in the levels of circulating catecholamines which in turn increase sympathetic tone and promote systemic vasoconstriction.In recent times,the detrimental role of the Renin Angiotensin system(RAS)has been elucidated in cases of CHF.The RAS is activated in CHF,directly or indirectly,producing vasoconstriction and leading to an increased production of aldosterone which causes retention of salt and water.Activation of the RAS also plays a central role in the pathogenesis of hyponatremia observed in severe CHF,and appears to be related to the degree of hypokalemia observed.Angiotensin II contributes

to the systemic vasoconstriction of CHF and the chronic inhibition of the RAS may have a salutatory effect on cardiac performance in such patients.Initially it was believed that only those patients whose CHF was associated with a high plasma renin activity(PRA)could benefit from the inhibition of the RAS, but,long term results have shown that angiotensin converting enzyme inhibitors could be used with encouraging results in at least 50% of patients with a low PRA CHF.

The most noteworthy and widely used drugs for therapeautic intervention are a group that block the conversion of the decapeptide Angiotensin I to the octapeptide Angiotensin II by peptidyl dipeptidase(converting enzyme)and hence known as "Converting enzyme inhibitors".The search for orally efficacious such drug culminated in the development of the highly active drug Captopril(Cushman et al,1970).

Captopril,by lowering production of the vasoconstrictc Angiotensin II,as well as favourably increasing bradykinin and two series prostaglandin(PGI_2)parameters decreases the systemic vascular resistance and enhances vascular responsiveness,thus relieving the excessive afterload observed in CHF.Captopril also reduces the secretion of the sodium retaining/potassium wasting hormone aldosterone,thereby contributing to preload reduction by controlling volume expansion and greatly lowering the risk of hypokalemia.In addition,Captopril redistributes regional blood flow,and improves renal blood flow and glomerular filtration. This promotes natriuresis and potassium conservation.Diuresis is increased and diuretic requirements are decreased with captopril.

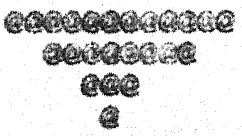
Captopril is a balanced vasodilator and could be ideal in most cases,it can also be used with added advantage in CHF secondary to hypertensive heart disease as it decreases the mean arterial pressure.Other noteworthy effects of captopril include reduction in the levels of circulating catecholamines,activation of the production of vasodilating prostaglandins and decrease in vassopressin secretion.The reports on the long term,relative and comparative effects of captopril in CHF are encouraging.

Interestingly further,the results of a very recent study conducted by the Captopril Digoxin Mulicenter Research Group have shown captopril therapy to be significantly more effective than placebo and placed it as an alternative to digoxin treatment in patients with mild to moderate heart failure who are undergoing maintenance diuretic therapy.

Not many studies have been undertaken in this country on the effects of vasodilator therapy,and the blockade of the RAS in particular,as an approach to therapy of CHF.Most studies here and abroad are based on hemodynamic measurements, the facilities for which are lacking in most Indian hospitals as well as ours.In patients with heart failure,the degree of cardiac dysfunction does not always correlate with the extent of symptomatic benefit.Furthermore,changes in central hemodynamics are not accompanied by similar changes in patients symptoms,as seen on response to treatment.Besides,a lack of correlation between the short term hemodynamic effects of captopril and susequent clinical response have been observed.

Also, the results of a clinical study on the long term effects of vasodilators as adjuvants in the therapy of CHF using Isosorbide dinitrate and/or Hydralazine conducted by Mishra DN et al in 1986 at our institution have been positive and encouraging.

These factors prompted us to undertake this clinical study on the comparative effects of therapy of CHF with captopril and digoxin, as well as to reassess the role of captopril as an adjuvant to the conventional decongestive therapy, wherever the role and use of digoxin is found mandatory and otherwise; and also in cases of CHF refractory to digoxin and diuretics.



REVIEW OF LITERATURE

REVIEW OF LITERATURE

Sir Thomas Lewis had defined heart failure as an inability of the heart to discharge its contents adequately. Sir Paul Wood defined it as a state in which the heart fails to maintain an adequate circulation for the needs of the body despite satisfactory venous filling pressure.This definition did not include insufficieht venous return as a cause for inadequate cardiac output.It is difficult for a single definition to suffice for heart failure,as clinical and physiological criteria essentially differ.

From a clinical viewpoint,Heart failure may be considered as a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues of the body.

In the intact heart,the cardiac output is normally regulated by an intimate integration of four principal determinants -preload,afterload,contractility and heart rate,.

The management of heart failure aims at the therapeautic manipulation of the above mentioned determinants of cardiac performance to provide optimal circumstances for the depressed contractile force or mechanical derangement of the failing heart to deliver a normal,or near normal cardiac output.

The cause of heart failure is usually diminished ventricular contractility owing either to direct myocardial damage(as in ischemic heart disease and primary

cardiomyopathy)or chronic pressure or volume overload(as in hypertension and valvular heart disease).

It was as early as 1922 when Wiggers and Fiel discovered that chronic heart failure was associated with increased systemic vascular resistance which resulted in increased afterload,causing reduction in stroke volume.It was later found that different forms of heart failure were associated with one or more of the following:i)increased neurogenic vasoconstrictor tone(i.e.,neuronally released norepinephrine),ii)increased hormonally released vasoconstrictors (eg norepinephrine or angiotensin),and iii)altered smooth muscle reactivity(eg increased responsiveness to metabolic vasodilator stimuli)(Zelis et al,1976,1978).

When the heart fails as a pump,a number of neurohumoral mechanisms are activated in an attempt to maintain cardiac output,and thus perfusion of the vital organs of the body(Cohn et al,1981):i)the body appears to utilise the Frank Starling mechanism whereby,a rise in end-diastolic volume(preload)is followed by a rise in cardiac output.This increase in preload is achieved by a combination of volume expansion,decrease in capacity of the vascular bed,and redistribution of blood flow.This results in part from the activation of the sympathetic nervous system(Levine et al, 1982),ii)the increased release of catecholamines by adrenergic cardiac nerves and the adrenal medulla which augments cardiac contractility,and iii)myocardial hypertrophy with or without dilatation,and iv)activation of the RAS.Renin secretion is

enhanced by a fall in perfusion pressure,and heightened sympathetic stimulation(Kluger et al,1982).

The Renin Angiotensin System:The RAS provides a fundamental physiological mechanism for the maintenance of blood pressure and perfusion of vital organs.It responds to changes in the perfusion pressure of the kidneys,and to volume,and achieves the adjustments by bringing about changes in both fluid volume and vascular tension.The renal enzyme 'renin'is secreted by the juxtaglomerular cells.The stimulus for renin release appears to be 3 fold:i)First,any factor tending to lower renal perfusion pressure,ii)the ionic environment of the tubular fluid,iii)through sympathetic nervous system mediated stimulus. This hormone reacts with a glycoprotein substrate to form the inactive compound angiotensin II.The "Converting enzyme" (Peptidyl dipeptidase)catalyses the conversion of angiotensin I to angiotensin II which is a highly active compound mediating the effects of the RAS.This phylogenetically ancient mechanism achieves its goal by i)Direct systemic vasoconstriction. Angiotensin II is a powerful systemic vasoconstrictor acting predominantly on the precapillary arterioles,and to a lesser extent on venules,ii)Facilitation of the effects-both central and peripheral,of the sympathetic nervous system by a predominant presynaptic facilitatory effect on adrenergic neurone terminals(Zimmerman,1981),iii)Promoting renal sodium retention through aldosterome and intrarenal hemodynamic changes whilst preserving glomerular filtration.Recent evidence suggests that angiotensin II may directly increase sodium resorption in the proximal tubule,and that,this effect can be

reversed by captopril(Dusing et al,1985),iv)By stimulating thirst and enhanced synthesis of vassopressin.

The RAS in Heart Failure:Whilst the RAS serves the body admirably in coping with day to day physiological changes, when pathological processes supervene,its activity may be counterproductive so that interrupting it provides a valid line of therapy in CHF.

Disturbances of the RAS have been described for over 40 years(Merill et al,1946;Davis JO,1965;Genest et al, 1968).They have been related to various factors including reduced perfusion pressure(Schneider et al,1973),reduced renal blood flow(Davis JO,1973;Davis JO,Freeman H,1976;Levine et al, 1979),and have been said to vary with the stage or rate of development of decompensation(Brown et al,1970;Turini et al, 1978).The end result was differently viewed either as a compensatory mechanism(Zelis R,Mason DT,1970)to help maintain arterial pressure despite a falling cardiac output,or as a potentially harmful vicious circle in which peripheral vasoconstriction and secondary aldosteronism led to further cardiac overload(Davis JO,1980).

The sympathetic nervous system and the RAS are activated in CHF although sympathetic stimulation may be one of the factors contributing to renin release.The increased sympathetic activity in CHF may represent an initiating factor in depression of cardiac output,the increasing vasoconstriction adversely limiting forward flow(Levine et al,1982).The increased levels of plasma norepinephrine are inversely related to baseline cardiac function,but the norepinephrine

levels do not change significantly with specific therapy (prazosin).On the other hand,the RAS was found to exhibit a wide spectrum of activity and hemodynamic improvement with captopril was related to this activity(Kluger et al,1982).

The sympathetic nervous system and the RAS thus combine to cause volume expansion and salt & water retention, and reduced vascular capacitance by the pressor actions of catecholamines and angiotensin.Whilst the cardiac output may tend to be favoured by these effects by the Frank Starling mechanism,they may be on balance more deleterious to the clinical state of the patient than helpful.First,the end-diastolic pressure may rise excessively with little added benefit to cardiac output,so that,the predominant clinical abnormality is high filling pressure with consequent pulmonary congestion.Secondly,the retention of salt and water may become so excessive that it serves no useful function, causes oedema and becomes an added burden to the already failing heart.Thirdly,and perhaps most importantly,the arteriolar constriction and consequent increase in the systemic vascular resistance causes an increase in afterload.This in turn tends to depress the cardiac output and thus affect the myocardial oxygen demand to supply ratio adversely.The important role of systemic vascular resistance has been established as a sustaining factor in chronic CHF(Ross J Jr, Braunwald E,1964).Systemic arterial pressure may be maintained at the cost of further deterioration in cardiac function.The latter point may be particularly pertinent in patients recieving treatment in the form of diuretics or

sodium restriction which may themselves stimulate further renin secretion(Hollenberg & Williams,1981).

Till a few years from now,the use of digoxin and diur-etics has been the mainstay of pharmacotherapeautic approach against CHF.In 1799,John Ferriar was the first to ascribe to digitalis a primary action on the heart.It is undoubtedly the earliest known inotropic agent which was deemed effective in CHF,and has so far been in use despite several disadvantages like a low therapeautic-toxic ratio,limited plasma concentration and modest inotropic action.This has been so mainly because of a lack of alternative modes of therapy.Digoxin principally increases cardiac contractility and reduces the heart rate, and the diuretics,decrease the preload and reduce pulmonary congestion.

More than 25 years ago it was suggested that the sustained decrease in heart size by diuretic treatment may in and itself,produce long term clinical benefit(Gorlin R,1962). The roughly 200 years of experience with digitalis cannot be regarded as typical of inotropic drug therapy for the very good reason that its salutatory effects are most often obvious in patients with atrial fibrillation where it is acting as an antidysrrhythmic agent(Mc Haffie et al,1977).It is now held that cardiac glycosides may not improve cardiac performance when added to rigorous diuretic therapy.The long term effect of digoxin in patients of heart failure with atrial fibrillation is well known,but long term clinical or hemodynamic benefit could not be shown or was infrequent in

patients with sinus rhythm(Johnson GD,Mc Devitt,1979).In fact, the efficacy of digoxin in patients of CHF in sinus rhythm is believed by many to be non-existent.Cardiotonic drugs though they increase renal blood flow,have been shown not to alter the ratio of renal blood flow(RBF)to cardiac output (Sandler et al,1961;Mc Donald et al,1964;LeJemtel et al, 1980;Cogan JJ,1980).Digoxin is also a toxic drug with a low therapeautic-toxic ratio and it has become debatable whether the benefits of using it outweigh the risks associated with its use(Selzer A,1981).The inotropic drugs have also been shown to have a tendency to cause or worsen ventricular arrhythmias whereas ACE inhibitors decrease ventricular ectopy(Cleland et al,1984;Packer et al,1984).Two recent studies have also shown that the use of inotropic drug results in short term symptomatic relief at the cost of accelerated deterioration in cardiac function(Packer et al,1984;Shah et al, 1985).There is broad agreement that the agents of first choice in the management of CHF are the diuretics.Unfortunately,the use of increasing doses of diuretics is subject to the law of diminishing therapeautic returns,the limiting factors being either drug toxicity or resistance to its effect.Studies have shown that the major cause for diuretic refractoriness is the activation of the RAS by these drugs(Ikram H et al,1980). Diuretic activation of the RAS leads to exacerbation of the arteriolar vasoconstriction with consequent decrease in cardiac output,and salt retention.It was thought possible later,that addition of an ACE inhibitor with diuretics could result in

further increase in exercise capacity by nullifying this effect (Bayliss et al,1977).

The combination of digoxin and diuretics does not alter the afterload.Diuretics,in addition,may precipitate low cardiac output since they decrease venous filling pressure.As such,this combination has been found inadequate in a large number of cases of CHF.

In the last decade or so,the clinicians have tried to alter the afterload favourably with the use of vasodilators.

The principal of peripheral vasodilatation in relieving pulmonary congestion was first postulated by Sarnoff & Farr as early as 1944.These drugs were first used in clinical practice by Burch in 1956 in CHF to decrease venous tone.With the same physiological principles in mind,Johnson et al(1972), employed sublingual nitroglycerine to induce peripheral vasodilatation for the relief of pulmonary oedema in patients of left ventricular failure.In both these studies,the objective was to decrease pulmonary congestion by venodilatation.At that time,the role of vasodilators in decreasing impedance of the left ventricle with subsequent increase in cardiac output was not appreciated.

Majid et al,1971;used phentolamine in patients of CHF developing after acute myocardial infarction and demonstrated substantial decline in systemic vascular resistance (SVR)and pulmonary arterial pressure,with increase in cardiac output,and without any significant changes in systemic arterial pressure and heart rate.Modern era of afterload reduction in the

treatment of CHF was thus begun by successful use of vasodilator in acute forward failure. Thereafter, the vasodilator therapy concept spread rapidly and extended to the management of severe chronic CHF also.

The beneficial effects of vasodilators are principally by their actions on the peripheral vascular bed. The vasodilators decrease pulmonary congestion by reduction of ventricular preload and increase cardiac output by reducing impedance to forward flow(Cohn, 1973). Furthermore, improvement in pump function produced by vasodilators is generally accompanied by decreased myocardial oxygen demand. This is because of reduced myocardial wall tension through Laplace Law. In contrast, an inotropic agent increases this demand by enhancing velocity of fibre shortening. This may be of particular importance to the patient of ischemic heart disease(Franciosca et al, 1977).

Neither the hemodynamic effects of heart failure nor those of vasodilators are uniform, and in view of the spectrum of action of vasodilator drugs, the choice of the drug should be based according to the predominant and specific deficits present in a particular patient(Braunwald E, 1977; Chatterjee & Parmley, 1977). Examples of predominant venodilators include nitroglycerine and nitrate, while on the other hand, hydralazine, nifedipine and minoxidil are predominantly arteriolar dilators.

Hemodynamic improvement in CHF with the use of Isosorbide dinitrate(Williams et al, 1977; Ghosh et al, 1977); after long term therapy with nitrate and hydralazine(Leier et al, 1981; Mishra et al, 1985-86 at our institution); with the use

of hydralazine alone(Chatterjee etal,1976)is well documented. The fear of clinically meaningful nitrate tolerance was found to be unfounded(Franciosca et al,1978).This seems to be true for hydralazine as well,because,the hemodynamic responses to this drug were also found to be unchanged after therapy, lasting on an average 8 months(Chatterjee et al,1978).

The examples of drugs having both arteriolar and venular dilating properties are sodium nitroprusside, phentolamine,phenoxybenzamine,prazosin,trimazosin,captopril and enalapril.Beneficial hemodynamic effects of sodium nitroprusside in patients of CHF due to mitral regurgitation has been observed(Chatterjee et al,1973).Prazosin and trimazosin have been shown to be of clinical benefit in CHF of varied etiology(Arnow & Danhey,1978).Beneficial effect of oral prazosin with acute and chronic use was also reported by Awan et al,1977.Prazosin,however,was found to be associated with drug tolerance(Packer et al,1978;Arnold et al,1978).

A comparative hemodynamic study was conducted by Leier et al in 1981 to evaluate the effects of hydralazine and isosorbide dinitrate alone and in combination in chronic CHF.They observed that hydralazine alone produced benefit as compared to isosorbide dinitrate,and their combination too was superior to the use of isosorbide dinitrate alone. Benefit of such a combination was reaffirmed by Kothiala et al in 1983.

Hemodynamic improvement with the use of nifedipine in chronic CHF is known(Leier et al,1984).Hemodynamic benefit, increase in duration of exercise have been noted with the use

of felodipine,a calcium channel antagonist with selective vasodilator property,in cases of chronic CHF(Temmis et al, 1984).

Empirically,a hydralazine-nitrate combination may be thought to work well for most patients of CHF with more emphasis on the nitrate if the predominant symptoms are pulmonary congestion,and more emphasis on hydralazine if low output symptoms(eg oliguria)predominate.Continuous nitrates may be unnecessary for chronic therapy once the patient is stabilised.With this amount of research,vasodilator therapy was established as an important adjunct to the conventional therapy of CHF.

However,with further studies,it became evident that vasodilator therapy,whilst undoubtedly effective in short term could fail in the long term.This failure could be attributed to the activation of the counterpoised homeostatic systems which antagonised the vasodilator actions of these drugs(Ikram H et al,1980).Sodium nitroprusside and prazosin were found to have a stimulant effect on the RAS,and this could result in therapeautic failure if sustained.Another problem with these agents was of rebound deterioration on withdrawal.

From the above studies it became obvious that an agent with vasodilator properties and a capability to block the RAS selectively would prove ideal in majority of cases of CHF.The use of such a drug would prevent either diuretic induced or vasodilator induced activation of the RAS.Since development of tolerance is related to the activation of the RAS,such a drug would likely be effective for long periods.

In addition,the blockade of the RAS in a specific manner would be a very much physiological approach to counteract the hemodynamic derangements seen in cases of CHF.

Development of the ACE Inhibitors:As it became evident from the above mentioned facts,ACE inhibition could be viewed as the most practical pharmacologic means to block the effects of the RAS.The development of the ACE inhibitors was based on the observation that the vasoactive snake venom from Bothrops jarapa was capable of suppressing the angiotensin converting enzyme(Ondetti MA,1977).The amino acid sequence of this active peptide was identified and the synthetic peptide SQ20881, teprotide,was developed subsequently(Ondetti MA,1977;Cushman, 1978;Ferguson,1977).Later,it became possible to develop a compound of comparable affinity for the converting enzyme that could be given orally.This agent was SQ14225 or captopril (Ondetti MA,1977;Ferguson,1977;Cushman,1978).With its development,a highly active pharmacological agent was available to test the role of the RAS in situations where or whenever, it was contributing to the pathophysiology of cardiovascular disease.

Enalapril(MK-421)and enalaprilat(MK-422)are still recent compounds of this group lacking the sulfhydryl moiety that initially was felt to be responsible for many of the side effects of captopril.These drugs are on the verge of being launched into clinical use in this country.

Pharmacology and therapeautic consideration of the drug, captopril,used in this study are given briefly as follows:-

Captopril is absorbed rapidly from the GIT in normal

individuals,with detectable levels seen as early as 15 minutes following administration.Approximately,60-75% of an oral dose is absorbed(Kriplani,1980;Duchin,1982b).It is not known if captopril crosses the placenta in humans(Pipkin,1982).Captopril does not enter into breast milk of humans,levels are less than 1% of the blood levels because of minimal entry(Devlin,1981).Captopril and its metabolites are mainly excreted by the kidneys with a minor role for elimination in the faeces.The renal excretion of captopril is rapid,over more than80% of the 24 hour urinary excretion occurs within 4 hours after administration and is essentially complete within the first 24 hours.The primary mechanism of excretion is tubular secretion.The elimination half life of unchanged captopril has been established to be 1.7 hours(Duchin,1982).Captopril can be removed from the body by hemodialysis(Hirakata,1981).

Peak hemodynamic effect as manifest by reduction in systemic vascular resistance occurs at 60 minutes.The duration of action also follows well with the pharmacokinetics of unchanged captopril and averages about 4-6 hours(Cody,1982).

Mechanism of action of ACE inhibitors:Most data support the view that the beneficial effects of the ACE inhibitors in heart failure arise mainly from the reduction in systemic vascular resistance and left ventricular filling pressure.The major contribution to this effect is from the inhibition of the RAS and subsequent reduction in angiotensin II concentrations. However,the correlation between the immediate hemodynamic effects and the plasma renin activity(PRA)is modest.One recent study showed a linear correlation between the immediate

Hemodynamic improvement following captopril and the pre-treatment PRA in 100 patients, but failed to show any useful correlation after 1to 3 months treatment(Packer et al, 1985). This inconsistency has suggested that factors other than blockade of the RAS(angiotensin formation precisely) may be responsible for the effects of heart failure, but there is evidence accumalating that tissue levels of ACE and angiotensin II(particularly in the vasculature)are more important than plasma levels in determining the drug's effects. (Unger et al, 1985).

Other factors may be involved. First, these drugs bring about a reduction in circulating catecholamines which have been shown to correlate with the hemodynamic improvement (Cody et al, 1982), and elevation in plasma adrenaline has been found after their withdrawal(Nicholls et al, 1981). However, such findings have not been consistent(Faxon et al, 1981). The reduction in sympathetic activity must be considered as a possible important aspect of ACE inhibition in CHF.

The third mechanism whereby, a reduction in systemic vascular resistance may be accomplished by ACE inhibition is by the inhibition of the potent vasodilator bradykinin. However, the extent of the effects of ACE inhibitors on circulating bradykinin is not certain. It has been suggested that the effects are local than systemic, and the renovascular effects of bradykinin are not enhanced by captopril(Edwards & Patfield, 1985).

A further possibility is that the inhibition of kininase stimulates the production of the vasodilator prostaglandin, PGE_2(Nasjletti & Malik, 1979). Support for this

fact is provided by the observation that indomethacin has been shown to inhibit the vascular effects of ACE inhibitors (Swartz & Williams, 1982).

Whilst the reduction in systemic vascular resistance is probably the most important effect of ACE inhibitors in heart failure, the changes in fluid and electrolyte status brought about by modification of pathophysiological processes in the kidney also contribute to their beneficial effect. Some consider these to be fundamental to their therapeutic use in heart failure (Lipkin & Poole-Wilson, 1985). Reduction in the levels of plasma and urinary aldosterone is the most obvious mechanism by which sodium excretion may be enhanced (Creager et al, 1981) but reversal of angiotensins' renal tubular and intrarenal hemodynamic effects which result in sodium retention may be more important (Todd & Heel, 1986). The reported reduction in plasma and urinary vassopressin levels (Thibonnier et al, 1981) with prolonged therapy and the enhancement of renal prostaglandins may also contribute (Nasjletti & Malik, 1979).

Recently, the RAS has been implicated in the pathogenesis of hyponatremia observed in patients with severe heart failure. The pharmacologic effects of angiotensin II will tend to cause water retention (thirst stimulation, vassopressin release and intrarenal hemodynamic changes) and the rapid and sustained correction of hyponatremia by captopril provides evidence for the major role of the RAS in its pathogenesis. Of equal importance, it suggests that the mechanism of the beneficial effect of ACE inhibitors in CHF is not confined to a nebulous vasodilator property.

The first ACE inhibitor to be used in cases of CHF was teprotide.A reduction in SVR and a rise in cardiac output were reported with the use of intravenous teprotide by Curtiss et al,1978.

Turini et al(1979)gave captopril during cardiac catheterisation to 6 normotensive patients with refractory CHF. They observed that captopril could reduce both the afterload and preload,and improve cardiac function.They opined that it remained to be seen that whether these benefits will persist with chronic administration.

Davis et al(1979)used captopril in the capacity of an orally effective ACE inhibitor in cases of chronic CHF. The 7 cases studied by them had little or no relief in symptoms despite use of oral vasodilators(6 with hydralazine and 1 with prazosin).Beneficial effects-hemodynamic and clinical led them to conclude that captopril appeared to offer promise in the treatment of CHF and was worthy of further investigation.

Hemodynamic effects of captopril were evaluated in 10 patients of CHF(7 due to IHD,1 hypertension,2 of unknown etiology)by Ader et al(1980).In all their cases they found significant increases in cardiac output(average 28%),stroke volume(49%)and stroke work index(26%)along with decrease in pulmonary capillary wedge pressure(48%),indicating improved left ventricular function.Modest decreases in heart rate and mean arterial pressure were also seen.In 7 of these cases repeat hemodynamic studies revealed sustained effects.These were accompanied by clinical improvement and increased exercise tolerance during maintenance therapy.They also suggested on basis

of their observations that tachyphylaxis does not appear to the effects of captopril in CHF.

Creager et al(1981)studied the acute effects of captopril on regional blood flow,renal hemodynamics and sodium excretion in 12 cases of severe CHF.The SVR was found to fall by 27% and the cardiac index to rise by 16%.There was no significant change in the glomerular filtration rate(GFR),the filtration fraction decreased significantly while urinary sodium excretion doubled.Captopril reversed the renal vasoconstriction in CHF and redistributed regional blood flow. The plasma aldosterone and norepinephrine concentrations showed a fall.Similar acute hemodynamic effects had been reported by Faxon et al in 1980.Creager et al also found that with captopril, the fraction of the cardiac output measured as renal blood flow was increased significantly to 14%.

The long term effects of captopril treatment were assessed by sequential hemodynamic measurements over a period of 6 months in 19 patients with resistant CHF by Fouad et al, 1982.Improvement was noted within the first week in 11 of the cases and was marked by a significant increase in cardiac output and stroke volume,a decrease in heart rate and total peripheral resistance.By the end of 3 months,7 of the remaining 8 also improved.The results suggested that the response to captopril may occur gradually,and the reduction in plasma aldosterone to PRA ratio was an effective marker of compliance.

Walsh & Greenberg(1981),Packer et al(1983),Kothiala et al(1983),Massie et al(1984)corraborated that hemodynamic and echocardiographic studies may not be essential in clinical

practice and that there was lack of definite correlation between hemodynamic value and long term clinical response.

Studies of Cohn and Franciosca(1977)revealed that vasodilators were of relatively less value in cases of obstructive valvular lesions as MS & AS.They were also found to be of lesser value in cases of chronic obstructive airway disease(Rubin et al,1982;Konstam et al,1984).

Cowley et al(1982)performed a placebo controlled study of captopril therapy in 10 patients with severe CHF whose symptoms were not controlled by digoxin and diuretics.Improvement was noted in exercise performance which was found to correlate with the reduction in the forearm vascular resistance caused by captopril.

Angiotensin II levels,hemodynamics and sympatho-adrenal function after low dose captopril im 10 patients of chronic CHF were studied by Cleland et al in 1984.9 of these patients had a high concentration of plasma renin.Frequent measurements were made over 60 minutes of a small dose(6.25 mg) and related to concurrently measured hemodynamic variables. Captopril was found to cause a decrease in systemic and pulmonary arterial pressure and an increase in the cardiac index. these changes coincided with reduction in concentration of plasma angiotensin II and increase in plasma concentration of renin.The hemodynamic changes were accompanied by a decrease in plasma epinephrine concentration.The patients with low plasma renin concentration were noted to show little hemodynamic response to the drug.Overall,captopril was found to improve the

altered hemodynamics in CHF with the observation that the first dose may produce hypotension.Vasomotor syncope with bradycardia had earlier been noted to occur after captopril in cases of CHF associated with a high PRA.

The largest,most significant and most widely quoted trial of captopril in heart failure was carried out by the Captopril Multicenter Research Group in 1983.92 patients with heart failure refractory to digoxin and diuretics were allocated to either captopril or placebo randomly.The clinical course and repeated exercise testing was recorded for 12 weeks.At the end of the 12 week period,the groups had been reduced for various reasons-47 on captopril and 28 on placebo.Using the NYHA functional class rating,30 captopril treated patients had improved compared to 10 of placebo group.In the captopril treated group,there was a mean 24% increase in the exercise duration but none in the placebo group.Pre- and post treatment radionuclide left ventricular ejection fraction data on 33 captopril and 16 placebo patients showed a mean improvement of 16% in the captopril group and virtually no change in the placebo group.An analysis of subjective assessments of improvement by doctor showed that about 80% of the captopril group and 30% of the placebo group had improved.

Packer et al(1984)investigated the efficacy of captopril in low renin CHF.They evaluated the long term hemodynamic and clinical responses to captopril in 26 cases of severe chronic CHF whose pretreatment PRA was less than 2 ng/ml/hr.After 2 to 8 weeks of continuous treatment,14

patients showed long term hemodynamic benefits, 14 cases developed sustained reactive hyperreninemia. 12 of these improved clinically. 12 other patients had no reactive rise in PRA and these showed no significant improvement in any hemodynamic variable. They thus concluded that many of the patients of CHF with a low PRA could benefit from captopril, and these patients could be distinguished from the non-responders by the occurrence of reactive hyperreninemia during long term treatment.

Cleland et al(1984)performed a double blind crossover study of captopril and placebo in patients with severe heart failure. During the double blind phase, captopril was found to be significantly better than placebo in relieving the symptoms of heart failure, increasing exercise duration, reducing end-systolic and end-diastolic ventricular dimensions and the incidence of ventricular extrasystoles. Adverse effects ~~we~~ were not troublesome but two patients developed mild postural hypotension initially. There was a rise in the effective renal plasma flow and a significant reduction in creatinine clearance. Serum and total body potassium increased. The workers concluded that captopril corrects biochemical abnormalities, limits arrhythmias, improves cardiac performance and benefits patients symptomatically in CHF.

Bayliss et al(1985)assessed 19 patients of chronic heart failure before and after acute and long term(4 weeks) treatment with captopril, and prazosin, given in random order. During captopril, hemodynamic improvement was maintained by the inhibition of the RAS. During prazosin, a decrease in SVR was

maintained,but,the PRA,aldosterone and norepinephrine concentrations increased,fluid retention developed and clinical benefit did not occur.

The Captopril Multicenter Research Group performed another study on the hemodynamic responses and long term effects of captopril in 124 patients of heart failure resistant to digoxin and diuretics.The cardiac status of these patients was deteriorating prior to this study.Favourable acute hemodynamic effects occurred consistently with captopril. Maximal mean % increases in cardiac index,stroke index and stroke work index were 35%,44% and 34% respectively.At 8 weeks, hemodynamic changes were sustained.Significant and sustained improvements were observed in most patients as measured by change in NYHA Class(79%).Those patients who underwent pre- and post treatment exercise stress testing,exhibited a highly significant increase in mean exercise tolerance time of 34%. There was no evidence of tachyphylaxis over a 18 month period. All patients with hypokalemia at entry and all but one with hyponatremia normalised rapidly.Dissappearance of oedema in 55% for whom data were available was a notable feature.Captopril was generally well tolerated although hypotension caused withdrawal of the drug in 6%.

The effect of intravenous captopril in patients with severe cardiac failure was studied by Rademaker et al in1986.A rapid reduction in SVR and systemic blood pressure were noted, and the cardiac output increased by 20%.The rapid response to intravenous captopril indicated that it could be useful for patients with severe heart failure requiring intensive treatment.

Bocanelli et al(1986)compared an addition of captopril(12.5 to 50 mg b.d.)with increasing doses of frusemide(25-100 mg/d)in CHF,in a randomised double blind comparative trial.Statistically significant improvement occurred in both the groups in a parallel fashion.Echocardiographic data showed significantly better pattern of changes in the captopril group.They concluded that the addition of low doses of captopril to basal therapy appeared to be as effective as addition of higher doses of furosemide in uncontrolled moderate CHF.This approach with captopril,at the same time appeared to be more physiological and safe.

Takada et al(1986)gave captopril 25 mg to 7 patients of chronic obstructive pulmonary disease in stable state. Captopril increased cardiac output by 23% and decreased mean systemic pressure by 12% but did not alter the mean pulmonary arterial pressure.The heart rate,mean right atrial,and pulmonary capillary wedge pressure remained unchanged.Pulmonary and SVR fell respectively by 14% and 31%.

Packer et al(1986)compared the short and long term clinical responses to sequential therapy with prazosin and captopril.The initial increases in stroke volume and cardiac index with prazosin were lost in the long term.Captopril produced modest increase in both these variables,and there was no attenuation of these effects on prolonged therapy.They proposed thus,that the choice of vasodilator drug over another in patients with CHF should be based on studies that compare their long term rather than short term effects.They attributed the superiority of captopril to its ability to effectively

reduce the activity of the sympathetic nervous system and the RAS.

Packer et al(1986)also investigated the adverse effects of captopril and enalapril therapy in CHF.They found that symptomatic hypotension,functional renal insufficiency and hyperkalemia were the 3 most common adverse effects which were predictable consequences of interfering with the RAS. They also found that these adverse effects could be prevented or reversed by increasing the intake of salt or decreasing the dose of comcomitantly administered diuretics.The occurrence of these side effects rarely caused discontinuation of drug.

Alicandri et al(1986)compared captopril and digoxin in mild to moderate heart failure.Captopril(25 mg 8 hourly) appeared to improve hemodynamic effort tolerance and cardiac function under stress of isometric exercise in patients with severe chronic CHF.The improvement was comparable to that obtained in the same subjects with digoxin(0.25 mg once daily) given for one month.They concluded that captopril with its lower toxicity and under therapeautic range was a valid and useful alternative to digoxin for treatment of patients of mild to moderate CHF in sinus rhythm.

Magnani & Magelli(1986,for Multicenter Research Group on mild heart failure)enrolled 94 patients of chronic CHF(NYHA Class II-IV)on digoxin for a 12 month trial in a random,double blind,placebo controlled study.After a placebo run in period,patients were assigned to placebo or captopril 25 mg tds.Digoxin was continued whereas diuretics were withdrawn.No significant differences were seen in the

trend of survival curve in the placebo or captopril treatment groups after 6 months. Patients treated with captopril without addition of diuretics had a significant improvement in NYHA Class, increase in exercise capacity, a decrease in CT Ratio and enhanced echocardiographic left ventricular contractility. These preliminary results proved captopril useful as compared to placebo in mild to moderate heart failure. Addition of captopril was held to form an useful adjunct and alternative to the addition of diuretics when the patient was ∠ on digoxin. No tachyphylaxis was observed.

Therapeautic evaluation of captopril was carried out by Mishra et al in 1986. 18 cases of resistant CHF who had recieved conventional therapy for at least 6 weeks including the use of vasodilators without significant relief, were added captopril (12.5 mg initially increasing to a maximum of 150 mg/d). At 2 months, 12 cases (66.6%) showed good response (decrease in NYHA Class by ≥2 grades), 4 fair response (decrease of 1 NYHA grade), and 2 did not respond. Unlike vasodilators, clinical and hemodynamic benefit was achieved without fluid retention in a physiological manner.

Kaushik et al (1986) reported experience with long term therapy of severe CHF (NYHA IV) in 8 cases not responsive to conventional therapy. All patients showed significant and comtinuing functional improvement within 2 weeks of start of therapy. There was an accompanying decrease in heart rate, mean arterial pressure and heart size. Left ventricular ejection fraction increased serially to statistically significant levels at 16 weeks.

In a randomised double blind trial,60 patients with left ventricular dysfunction(ejection fraction less than 45%)but without clinical evidence of heart failure,1 week after Q wave myocardial infarction,were given captopril 25 mg tds, frusemide 40 mg od or placebo by Sharpe et al(1988).With captopril,the left ventricular end systolic volume index and ejection fraction were significantly increased from 1 month onwards.In contrast,the frusemide and placebo groups showed significant increases in ventricular volumes,with stroke volume index unchanged and ejection fraction slightly reduced.The study demonstrated that captopril could improve symptomless LV dysfunction in patients with acute Q wave myocardial infarction.

In contrast to these studies,the use of captopril in primary pulmonary hypertension has been dissappointing to suggest that angiotensin does not play an important role in the maintenance of this condition(Rich et al,1982;Leier et al,1983).

Of great interest is the study conducted by the Captopril Digoxin Multicenter Research Group which published its observations in 1988.This multicentric,double blind,placebo controlled study compared the effects of captopril treatment with those of digoxin treatment during maintenance diuretic therapy,in patients with mild to moderate heart failure.Compared with placebo,captopril therapy resulted in significantly improved exercise time(mean increase 82 s vs. 35 s)and improved NYHA Class(41% vs.22%),but digoxin therapy did not.Digoxin increased ejection fraction(4.4% increase)compared with captopril (1.8% increase),and placebo(0.9% increase).The number of premature

ventricular ectopic beats(PVC's)decreased 45% in the captopril group,and increased 4% in the digoxin group with more than 10 PVC's per hour.Treatment increased requirements for diuretic therapy,and hospitalisations were significantly more in cases recieving placebo compared with those recieving either active drug.Transitory hypotension occurred more frequently with captopril.The study concluded that captopril treatment is significantly more effective than placebo,and is an alternative to digoxin therapy in patients with mild to moderate heart failure in sinus rhythm,who are recieveing maintenance diuretic therapy.

This mass of data is telling the physicians that:- i)the ACE inhibitors are unique new type of therapy for heart failure,ii)they have an advantage over previous therapies of being capable of blocking sodium retention by the kidney which results in some advantageous correction of biochemical abnormalities,iii)their effects are detectable both by hemodynamic and moreso clinical parameters which may not always mutually correlate,iv)their effects are both acute and long lasting,v)they can be valid alternatives to digoxin in cases of CHF in sinus rhythm(mild to moderate),vi)their use can bring about reduction in diuretic dosages,vi)the ACE inhibitors may improve prognosis,a conclusion which has to be guarded, because,only cases refractory to other therapies have been studied in this regard,and vii)they are relatively well tolerated and safe drugs with a promising future.

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MATERIAL & METHODS

MATERIAL AND METHODS

The present study was carried out in the department of Medicine,M.L.B.Medical College,Jhansi.The case material of the present study consisted of patients having congestive heart failure admitted in the medical ward and/or attending medical OPD at the medical college.The period of study extended from August 1988 to July 1989.A total of 64 patients were observed during this period.These patients were assigned to 3 groups-A,B & C.Group A,the control group, had patients who recieved conventional decongestive therapy in the form of digoxin and diuretics.Group B recieved captopril and diuretics for treatment of CHF,all the cases kept in this group were in sinus rhythm and digoxin was not used in them.Group C patients recieved all the 3 drugs,i.e., digoxin,captopril and diuretics.Majority of the patients assigned to this group(82%)had severe chronic CHF which was deteriorating despite optimal doses of digoxin and diuretics.

The control group consisted of 22 patients out of which 15 were of valvular heart disease,3 of ischemic heart disease(IHD),and 2 each of congestive cardiomyopathy and cor-pulmonale.Group B had 20 patients of which 11 were of valvular heart disease,6 of IHD and 3 of hypertensive heart failure.The other study group,group C consisted of 21 cases of valvular heart disease and a single cases of congestive cardiomyopathy.

All cases were subjected to detailed interrogation

and clinical examination.The history of previous decongestive treatment was enquired in detail.Etiological diagnosis of congestive heart failure was confirmed by relevant investigations.

Severity of congestive heart failure at the initial examination was assessed by noting effort tolerance and the patients were grouped on the basis of NYHA classification. All patients had their routine blood(Hb,TLC,DLC,ESR) and urine analysis(routine and microscopic),blood urea,serum creatinine,blood sugar(fasting & post prandial),serum cholesterol,and SGOT,SGPT if required,done.X-Ray Chest and ECG was taken in every case.These investigations were repeated to monitor the prognosis as and when required.

The dose of captopril employed was 31.25 mg/day on an average and ranged from 6.25 mg to 75 mg/day.The drug was started with low doses and built up according to response and the side effects observed.Patients were asked to report about any side effects(nausea,vomiting,diarrhoea,headache, palpitation,postural giddiness,skin rash)if they ever experienced them.The dose of captopril was adjusted if required to produce the optimal response and to avoid adverse reactions.The patients of the control group recieved only digoxin and diuretics.The dosage of these drugs were adjusted according to the need of the patients.

The response to treatment was noted by observing the following parameters initially daily and then at weeks(weekly interval.The data obtained was recorded on specific proforma (appendix I)designed for the purpose of analysis and evaluation

of the results.

NYHA Class:Patients were graded according to NYHA(New York Heart Association)classification.

Class I: Patients with cardiac disease but with no limitation of physical activity.Ordinary physical activity causes no undue dyspnoea,anginal pain,fatigue or palpitation.

Class II:Patients with slight limitation of physical activity. They are comfortable at rest and with mild exertion.They experience symptoms only with more strenuos grade of ordinary activity.

Class III:Patients with marked limitation of physical activity. They are comfortable at rest but experience symptoms even with milder forms of ordinary activity.

Class IV:Patients with inability to carry out any physical activity without discomfort.Symptoms of cardiac insufficiency may be present even at rest and are intensified by activity.

24 Hour Urinary output:Patients were asked to collect their urine of 24 hours from the first day measured initially daily and later on at weekly intervals.

Weight:Weight was recorded to the nearest 0.5 kgs by using adult type of weighing machine.Same machine was used for subsequent follow-up to minimise instrumental error.

Heart Rate:The heart rate was recorded by auscultation at the chest directly.Duration of 1 minute was used for the record.

Blood pressure:This was recorded by mercury sphygmomanometer in lying and sitting position and in both upper & lower limbs if needed.

JVP: Jugular venous pressure was measured with patient propped up in bed in bed with his trunk,neck and head being in straight line and making an angle of 45° with the bed.Light was allowed to come and fall down on the neck tangentially.A scale was kept from the point of highest pulsation in internal jugular vein on right side towards manubrium sterni.Another scale was kept vertically from the angle of Louis.Vertical height of later scale in centimetres below the horizontal scale was taken as JVP.Depending on situation JVP was measured in other position also like 60° & 90°.

Liver size:Liver was measured in centimetres below subcostal margin in the mid-clavicular line.

Oedema:Oedema was recognised behind the malleoli of tibia and fibula of ambulatory patients and on sacrum who were confined to bed.Pressure of the finger was maintained for 30 seconds and pitting was noted.

Basal crepts:The lungs were examined for crepts by way of auscultation and monitored to see the effect of therapy on them .

Heart size:All patients had at least 2 X-Rays of chest done during the period of hospitalisation,one shortly after admission and other just before hospital discharge or during follow-up.If the patient was serious the X Ray film was taken in supine position but otherwise most of the films were exposed with the patients in upright position after inspiration at 6 feet distance.Cardiomegaly was assessed from the film by the cardiothoracic ratio,defined as the ratio between the transvers

diameter of the heart and internal diameter of the chest.The transverse diameter of the heart was obtained as the sum of the widest portion of heart from the right to the left border of cardiac silhoutte at the midline.Internal diameter of the chest was taken as maximal internal thoracic dimension taken at the level of the highest point on the left hemidiaphragm. CT Ratio above 0.5 was considered abnormal.

Pulmonary venous congestion on chest X Ray was graded.

Grade 0=No pulmonary venous congestion.

Grade I=Pulmonary venous hypertension defined as greater diameter of upper compared to lower lobe pulmonary vessels(film was taken in upright position).If the film was taken in supine posture, then pulmonary vascular redistribution and either peribronchial cuffing or loss of right hilar angle were taken as grade I.

Grade II:Interstitial pulmonary oedema defined as loss of pulmonary vascular marking in association with kerley B lines.

Grade III:Localised alveolar oedema defined as confluent alveolar infiltrates in perihilar area and lower lung field.

Grade IV:Diffuse alveolar oedema defined as diffuse confluent alveolar infiltrates throughout most area of both lung fields.

Clinical follow-up:The dosage of captopril was kept constant at discharge and patients were asked to attend the medical OPD for their evaluation at weekly intervals regularly.All the possible complicating events like side effects and drug toxicity, response to therapy(improvement/worsening of CHF) and death if it occurred were recorded.

OBSERVATIONS

OBSERVATIONS

The period of the present study extended from August 1988 to July 1989. A total of 64 patients of CHF were observed during this period. The patients were put into three groups - A, B & C. Group A comprised of 22 patients and served as the control group. The patients of this group recieved conventional decongestive therapy in the form of digoxin and diuretics. Out of these 22 cases, 9 were males and 13 females. The average duration of CHF was 1.30 years (range 0.08 to 8 yrs). In group B, one of the study groups, 20 patients out of which 8 were males and 12 females were studied. The patients of this group recieved captopril and diuretics for the treatment of their CHF. All these cases were in sinus rhythm and digoxin was not given to these patients. The average duration of CHF in this group was 1.15 years (range 0.02 to 5 yrs). In group C, the other study group, 22 cases were studied. Out of these 13 were males and 9 females. The average duration of CHF in this group was 2.69 years (range 0.04 to 8 yrs). 18 of these caes had already been on digoxin and diuretics for an average duration of 10 months and were poorly controlled with such therapy. Captopril was used as an adjuvant drug, i.e., in addition to digoxin and diuretics, for the treatment of CHF in this group.

The age and sex distribution of the cases of the control and study groups is shown in table I. In group A, the age ranged from 15 to 62 years (average 39.3 yrs), and from 20 to 65 years (average 42.2 yrs) & 10 to 62 years (average 33.18 yrs) in groups B & C respectively.

FIG. 1.

MULTIPLE BAR DIAGRAM SHOWING AGE WISE DISTRIBUTION OF THE CONTROL AND STUDY GROUPS

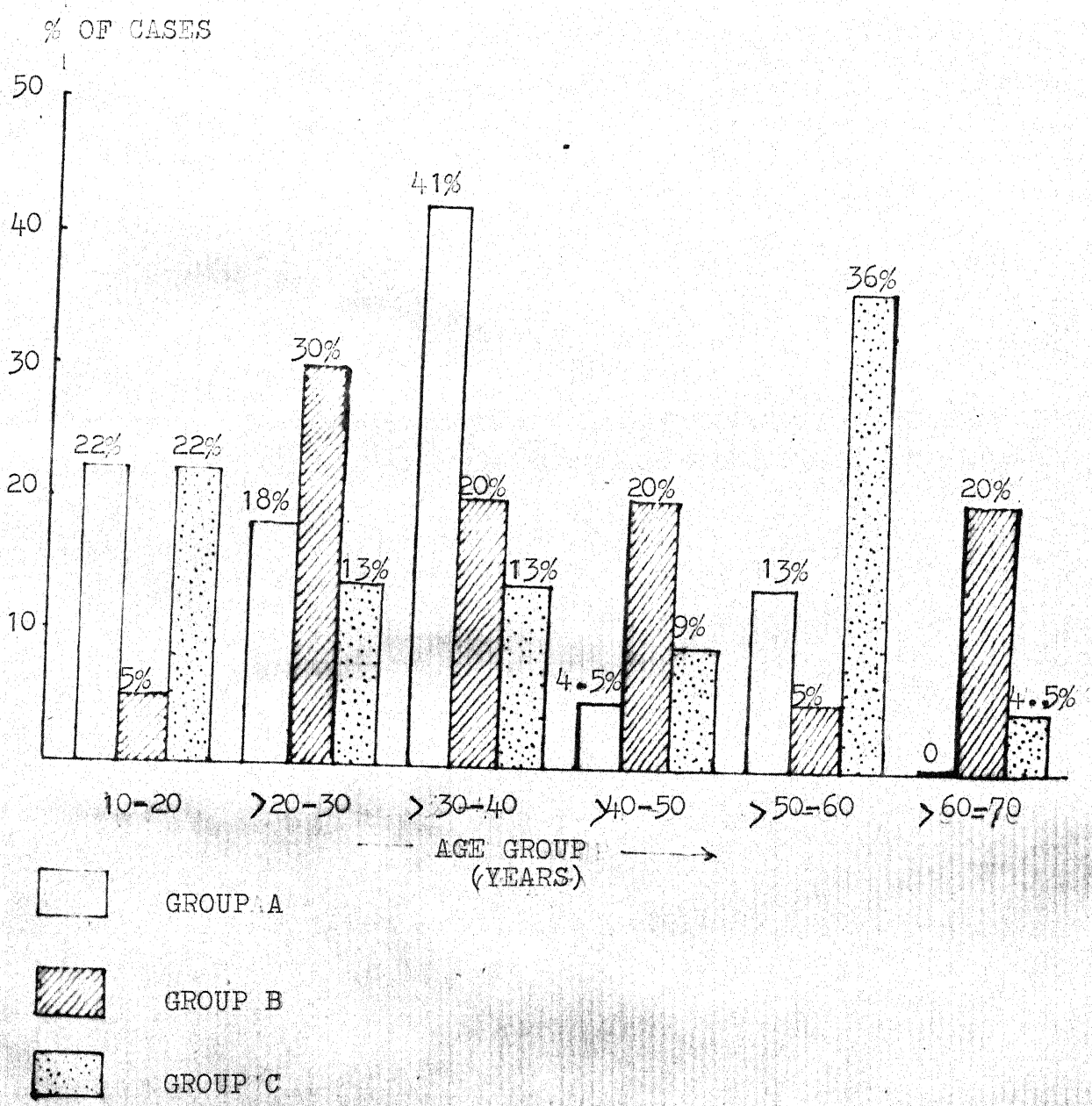
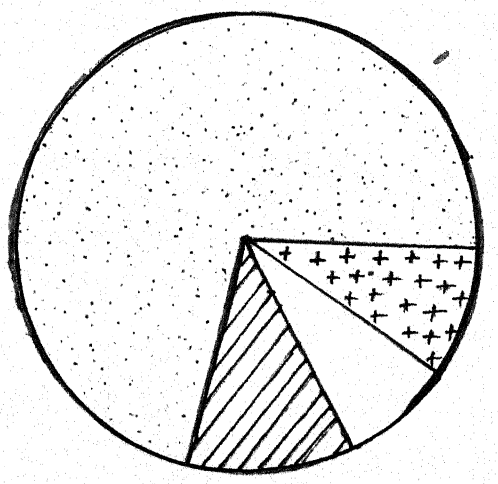
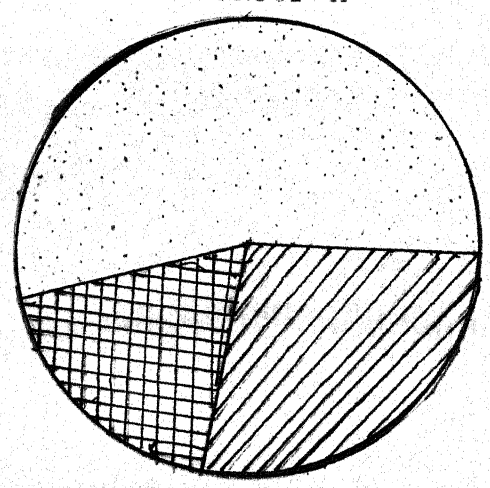


FIG. 2.

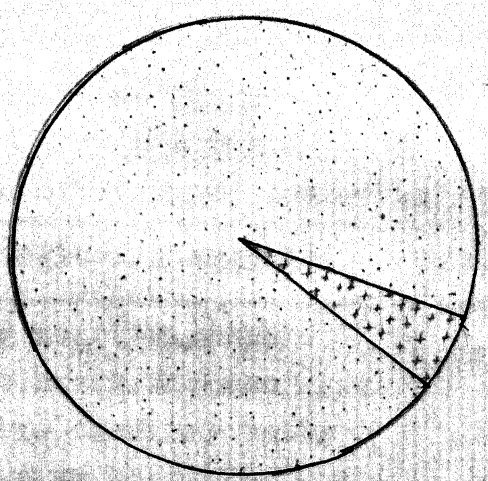
DIAGRAM SHOWING ETIOLOGICAL DISTRIBUTION OF CASES IN THE CONTROL AND STUDY GROUPS



GROUP A



GROUP B



GROUP C

VALVULAR HEART DISEASE

ISCHEMIC HEART DISEASE

HYPERTENSIVE HEART FAILURE

CONGESTIVE CARDIOMYOPATHY

COR-PULMONALE

TABLE I

Age and Sex distribution of the cases of control and the study groups

S No.	Age group (Years)	Group A T	Group A M	Group A F	Group B T	Group B M	Group B F	Group C T	Group C M	Group C F
1.	10-20 yrs	5	3	2	1	1	0	5	4	1
2.	> 20-30 yrs	4	2	2	6	1	5	3	1	2
3.	> 30-40 yrs	9	3	6	4	1	3	3	1	2
4.	> 40-50 yrs	1	0	1	4	1	3	2	1	1
5.	> 50-60 yrs	3	1	2	1	0	1	6	6	2
6.	> 60-70 yrs	0	0	0	4	4	0	1	0	1
	TOTAL	22	9	13	20	8	12	22	13	9

T=Total; M=Male; F=Female

The diagnostic break-up of cases is shown in table II. A significant number of cases were of valvular heart disease (15, 11 & 21 in groups A, B & C respectively) followed by ischemic heart disease (3 & 6 ingroups A & B). 2 cases of congestive cardiomyopathy were studied in group A and 1 in group C. 3 cases of hypertensive heart failure were studied in group B, and 2 cases of cor-pulmonale in group A.

TABLE II

Distribution of cases of control & study groups according to etiolo[gy]

S.No.	Etiological diagnosis	Group A	Group B	Group C
1.	Valvular heart disease	15	11	21
2.	Ischemic heart disease	3	6	0
3.	Congestive cardiomyopathy	2	0	1
4.	Hypertensive heart failure	0	3	0
5.	Cor-pulmonale	2	0	0

Further break-up of the cases of valvular heart diseases is depicted in table III. The most common lesion was mitral stenosis alone or in combination with mitral regurgitation.

TABLE III

Distribution of cases of valvular heart disease according to the type of lesion in the control and study groups.

S.No.	Type of lesion	Group A	Group B	Group C
1.	Mitral stenosis	10	3	6
2.	Mitral regurgitation	0	2	3
3.	Mitral stenosis + Mitral regurgitation	2	4	9
4.	Aortic valve disease	2	0	1
5.	Multivalvular disease	1	2	2
	TOTAL	15	11	21

The therapeautic response during short term(1 to 4 weeks)observation in terms of the effect of treatment on various objective parameters monitored is depicted for groups A,B & C in the tables IV,V & VI respectively. The response was observed objectively in the form of average increment in urine output, reduction in weight, change(decreases)in heart rate and blood pressure, decreases in JVP(Jugular venous pressure)and liver size, relief in pedal oedema and in pulmonary rales, decrease in heart size and pulmonary venous congestion on X-Ray Chest; and symptomatic improvement in Effort tolerance.

TABLE IV

Effect of therapy on various parameters in cases of the control group(Group A)on short term(1 to 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Avge Change
1.	Urine output ml/24 hours	450-1250 863.6±212.2	900-1600 1256.8±179.8	+393.1
2.	Weight Kgs	32-64.8 46.6±9.1	30.6-64 45.3±9.7	-1.3
3.	Heart rate beats/mt	70-140 104.6±18.8	76-116 94.4±11.9	-10.1
4.	Blood pressure systolic mm of Hg	90-140 107.8±13.0	90-150 108.1±6.0	+0.37
5.	Blood pressure diastolic mm of Hg	40-84 70.1±13.3	50-86 70.2±9.0	+0.09
6.	JVP cms	4-11 7.0±2.3	4-8.5 4.7±1.3	-2.3
7.	Liver size cms	0-7 2.7±2.1	0-4.5 1.1±1.2	-1.5
8.	Cardiothoracic Ratio (CT Ratio)	0.44-0.76 0.56±0.97	0.43-0.73 0.54±0.07	-0.02

Avge=Average ; JVP= Jugular venous pressure

TABLE V

Effect of therapy on various parameters in cases of the study group B on short term(1 to 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1200 866.5±206.9	1100-2000 1417.5±187.9	+551
2.	Weight Kgs	37.5-58 47.7±5.4	36-57.4 46±5.6	-1.6
3.	Heart rate beats/mt	96-132 104.9±11.9	72-104 87.8±8.1	-17.1
4.	Blood pressure systolic mm of Hg	100-190 127.4±26.5	96-160 118.3±15.7	-9.1
5.	Blood pressure diastolic mm of Hg	30-120 77.7±8.9	30-100 72.9±15.3	-4.8
6.	JVP cms	4-12 6.8±2.5	4-12 4.6±1.2	-2.1
7.	Liver size cms	0-8 2.9±2.3	0-6.5 1.0±1.4	-1.8
8.	Cardiothoracic Ratio (CT Ratio)	0.47-0.73 0.59±0.07	0.40-0.71 0.57±0.07	-0.02

TABLE VI

Effect of therapy on various parameters in cases of the study group C on short term(1 to 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1200 1006.8±121.4	900-1650 1306.8±204.1	+300
2.	Weight Kgs	33-72 50.2±11.3	31.8-67.8 48.4±10.9	-1.8
3.	Heart rate beats/mt	66-152 104.3±22.5	66-110 89.2±14.8	-15.0
4.	Blood pressure systolic mm of Hg	90-140 113.3±13.4	84-130 109.6±10.8	-3.7
5.	Blood pressure diastolic mm of Hg	30-90 71.5±15.1	40-82 70.2±11.0	-1.2
6.	JVP cms	4-15.5 9.1±2.8	4-12 5.1±2.3	-3.9
7.	Liver size cms	3-12.5 6.2±2.5	1-8 2.7±2.1	-3.5
8.	Cardiothoracic Ratio (CT Ratio)	0.46-0.80 0.63±0.09	0.43-0.74 0.59±0.08	-0.04

The effect of therapy in the control and study groups on the NYHA(New York Heart Association)Class,used to define Effort tolerance in this study,is shown in tables VII & VIII.

T A B L E VII

Effect of therapy on NYHA Class in the control and study groups on short term(1 to 4 weeks)observation.

NYHA Class	No.of patients Group A		No.of patients Group B		No.of patient Group C	
	I*	II*	I*	II*	I*	II
IV	9(41%)	0	9(45%)	0	13(59%)	0
III	13(59%)	3(13%)	11(55%)	3(15%)	9(41%)	2(9%
II	0	15(68%)	0	8(40%)	0	12 (54%
I	0	4(18%)	0	9(45%)	0	8 (36%

I*=Before therapy;II*=After therapy

T A B L E VIII

Effect of therapy on the improvement achieved in NYHA Class in the control and study groups on short term(1 to 4 weeks) observation.

Group	Good improvement (improvement by 2 or more NYHA grades)	Fair improvement (improvement by 1 NYHA grade)
A	50%	45.45%
B	70%	30%
C	68%	27%

EFFECT ON URINE OUTPUT:

The average urine output in the control group at the time of inclusion in the study was 863.3±212.2 ml(range 450-1250 ml),and increased to an average of 1256.8±179.8 ml (range 900-1600 ml)after therapy.The corresponding values in cases of group B,recieving captopril and diuretics were 866.5±206.9 ml(range 450-1200 ml)and 1417.5±187.9 ml (range 1100-2000 ml).In group C,the average urine output of 1006.8 ±121.4 ml(range 450-1200 ml)before therapy increased to an average of 1306.8±204.1 ml(range 900-1650 ml)after therapy. Thus the average increases recorded in these groups A,B & C on short term observation were +393.1 ml,+551 ml and +300 ml respectively.An inceases in urine output was recorded in all the cases of each of these groups.

EFFECT ON WEIGHT:

In the control group(A),the average weight at the time of inclusion in the study was 46.6±9.4 kgs(range 32-64.8 kgs).This was reduced to an average of 45.3±9.7 kgs(range 30.6 -64 kgs)after therapy,the average reduction in weight being -1.3 kgs.In group B,the average recorded reduction in weight was -1.6 kgs.The weight reduced from an average of 47.7±5.4 kgs before therapy to an average of 46±5.6 kgs after therapy.The range of weight in these were 37.5-58 and 36-57.4 kgs respectively.In the cases of group C,the average weight of 50.2±11.3 kgs(range 33-72 kgs)before therapy was reduced to an average of 48.4±10.9 kgs (range 31.8-67.8 kgs).The average reduction in weight in this group was -1.8 kgs.

A reduction in weight was seen in all the cases of group A. 1(5%) cases of group B and 1(4.5%) cases of group C did not record a reduction in weight.

EFFECT ON HEART RATE:

In the control group, the average heart rate at the time of inclusion in the study was 104.6±18.8(range 70-140) beats per minute, and after therapy in the short term was decreased to an average of 94.4±11.9(range 76-116) beats per minute, the average decrease being -10.1 beats per minute. In group B, the pre-inclusion average heart rate of 104.9±11.9 (range 96-132) beats per minute was decreased to an average of 87.8±8.1(range 72-104) beats per minute after therapy. The average decreases in heart rate was -17.1 beats per minute. In cases of group C, the heart rate decreased to an average of 89.2±14.8 (range 66-110) beats per minute after therapy, from a pre-inclusion average heart rate of 104.3±22.5(range 66-152) beats per minute. The average reduction in this cases was -15 beats per minute. 1(4.5%) cases of the control group did not show reduction in heart rate, in this cases the heart rate actually increased. 2 cases of group C also did not show a reduction in heart rate, in one of these the heart rate was found to increase and in the other it showed no alteration. In a single(5%) case of group B no change in the heart rate was seen.

EFFECT ON BLOOD PRESSURE:

In group A, the average systolic blood pressure at

the time of inclusion in the trial was 107.8±13 mmof Hg(range 90-140 mm of Hg).This showed an insignificant small rise to an average of 108.1±6 mm of Hg(range 90-150 mm of Hg),the average rise being +0.37 mm of Hg.The pre-inclusion diastolic blood pressure average of 70.1±13.3 mm of Hg(range 40-84 mm of Hg)also showed a small or rather minute rise to an average of 70.2±9 mm of Hg (range 50-86 mm of Hg),the average change being +0.09 mm of Hg.

In group B,4(20%)patients had raised(i.e.,greater than 140/90 mm of Hg)blood pressure at the outset.The systolic blood pressure in these cases ranged from 150-190 mm of Hg with an average of 172.5±17.8 mm of Hg,and the diastolic blood pressure ranged from 90-120 mm of Hg with an average of 105±11.1 mm of Hg. In non-hypertensive patients of CHF,the systolic blood pressure ranged from 100-140 mm of Hg(average 116.1±12.9 mm of Hg)and the diastolic blood pressure from 30-90(average 70.8±13.6)mm of Hg before therapy.In the hypertensive patients after therapy,the systolic and diastolic blood pressures came down to averages of 138±19.8(range 106-160)mm of Hg,and 87.5±16.3(range 60-100)mm of Hg respectively.The blood pressure normalised in two of these 4 hypertensive cases.Thus in cases of these 4 patients an average decrease of -34.5 mm of Hg in the systolic blood pressure and -17.5 mm of Hg in the diastolic blood pressure were noted. In the non-hypertensive patients,the average systolic and diastolic blood pressures at the time of inclusion in the study were 116.1±12.9(range 100-140)mm of Hg and 70.8±13.6(range 30-90)mm of Hg respectively.With short term therapy these were

seen to fall to averages of 113.3±9.5(range 96-130)mm of Hg systolic and 69.2±12.6(range 30-90)mm of Hg diastolic.Thus the average decreases seen in the systolic and diastolic blood pressures amongst the non-hypertensive patients of group B were -2.8 & -1.6 mm of Hg respectively.

In group C,the average systolic blood pressure at the time of inclusion in the trial was 113.3±13.4(range 90-140) mm of Hg,and the diastolic blood pressure 71.5±15.1(range 30-90) mm of Hg.After therapy on short term observation the average systolic blood pressure was 109.6±10.8(range 84-130)mm of Hg and the average diastolic blood pressure 70.2±11(range 40-82) mm of Hg.The average recorded reductions in the systolic and diastolic blood pressures thus were -3.7 and -1.2 mm of Hg respectively.

The blood pressure was seen to increase in 9(41%) cases of group A and fall in 7(32%)cases,in the remaining no significant alteration was seen.In group B,the blood pressure was found to decrease in 13(65%)cases,increase in 5(25%)cases and remain unchanged in the remaining 2(10%)cases.The blood pressure increased in 7(31%) cases of group C and decreased in 11(50%)cases,while it did not show any change in the rest.

EFFECT ON JUGULAR VENOUS PRESSURE:

In the control group,the average JVP was 7.0±2.3 cms range 4-11 cms)at the time of inclusion in the study,on short term,after therapy,this decreased to an average of 4.7±1.3 cms (range 4-8.5 cms),the average noted decrease being -2.3 cms. In group B,the JVP was found to decrease from an average of

6.8±2.5 cms(range 4-10 cms)to an average of 4.6±1.2 cms(range 4-10 cms),the average fall was -2.1 cms.In group C,the initial average JVP of 9.1±2.8 cms(range 4-15.5 cms)decreased to an average of 5.1±2.3 cms(range 4-12 cms),the average fall being -3.9 cms.

During short term observation JVP was showing a decrease in 6(27%)cases of group A while it normalised in 15(68%) cases.In group B,the JVP decreased in 5(25%)while it became normal in 9(45%)cases.21(95%)cases of group C recorded a fall of JVP while in 14(63.6%)cases it had become normal.

EFFECT ON LIVER SIZE:

The average liver size(as measured in centimeters below the subcostal margin in the right mid-clavicular line)was 2.7±2.1 cms(range 0-7 cms)in case of group A.This got reduced after therapy to an average of 1.1±1.2 cms(range 0-4.5 cms),the average reduction in liver size being -1.5 cms.In group B,the average liver size of 2.9±2.3 cms(range 0-8 cms)was reduced to an average of 1±1.4 cms(range 0-6.5 cms),the average noted decrease being -1.8 cms.Group C showed an average decrease of -3.5 cms where an average pre-inclusion liver size of 6.2±2.5 cms(range 3-12.5 cms) was reduced to an average of 2.7±2.1(range 1-8)cms.Only 2 cases of group C did not exhibit a decrease in liver size.Hepatomegaly regressed to an impalpable liver in 8(36.3%),5(25%) and 5(4.5%) cases of the groups A,B & C respectively.

EFFECT ON HEART SIZE:

The average CT Ratio of 0.56±0.07(range 0.44-0.76) decreased to an average of 0.54±0.07(range 0.43-0.73)after therapy in case of group A,the average decrease being -0.02.In group B,the average pre-inclusion CT Ratio of 0.59±0.07(range 0.47-0.73)was

reduced to an average of 0.57±0.07(range 0.40-0.71) after therapy during short term observation.The average reduction in heart size was -0.02.In case of group C,an average reduction of-0.04 was noted in the heart size.Here the pre-inclusion average heart size was 0.63±0.09(range 0.46-0.80)and after therapy 0.59±0.08 (range 0.43-0.74).A reduction in heart size was observed in 19(86.3%),18(90%) and 21(95%)cases of the groups A,B & C respectively.2 cases of group A did not show any change in heart size while in 1 case the size increased slightly;2 cases of group B and 1 case of group C did not reveal any alteration in heart size.

EFFECT ON PEDAL OEDEMA:

In the control group,oedema was present in 14(63.6%) cases at the time of inclusion in the trial.It subsided totally in 85% of these cases and was reduced in rest of the subjects. In case of group B,oedema was present in 13(65%)cases and dissappeared in 76% of these cases with treatment during short term observation.In all the other cases it was reduced in severity.In cases of group C,20(91%)cases had pedal oedema at the time of inclusion into the study.Dissappearance of oedema was seen in 85% of these patients after therapy,while in others except 2 of the cases the oedema was lessened.

EFFECT ON BASAL RALES:

Basal rales were present in all the cases of the groups A,B & C.A decrease in crepts was observed in 15(68%), and 10(50%) & 11(50%)cases of these groups respectively.Crepts completely disappeared in 6(27%),9(45%)and 7(31.8%)cases of these groups respectively.

EFFECT ON EFFORT TOLERANCE:

In the control group, there were 13(59%) cases in NYHA Class III and 9(41%) cases in NYHA Class IV. None of the patient was in NYHA Class I or II. After therapy, in the short term, 15(68%) of the cases were seen to fall in NYHA ClassII, 4(18%) in NYHA Class I and 3(13.6%) in NYHA Class III. None of the cases remained in NYHA Class IV. 11(50%) of the patients were showing good improvement in the form of improvement in NYHA class by 2 or more grades, while 10(45.5%) had shown fair improvement in the form of improvement in NYHA Class by one grade. Only 1(4.5%) cases who was in NYHA Class IV did not show any benefit.

In cases registered in group B, 11(55%) were in NYHA Class III and 9(45%) in NYHA Class IV. None of the cases was in Class I or II. After therapy, 9(45%) patients had come in NYHA Class I, 8(40%) in Class II, while 3(15%) in NYHA Class III. 14(70%) cases were showing good improvement (reduction in NYHA Class by 2 or more grades) and 6(30%) improved fairly (by 1 NYHA Class). Thus all the patients exhibited improvement in Effort tolerance in this group.

13(59%) of cases of group C were in NYHA Class IV and 9(41%) in NYHA Class III at the time of inclusion in the trial. With therapy in the short term, 12(54%) cases were seen to fall in NYHA Class II, 8(36%) in NYHA Class I and 2(9%) in NYHA Class III. 15(68%) of these had improved by 2 or more NYHA grades (good improvement) while 6(27%) by 1 NYHA Class (fair improvement). A single case who was in Class IV did not show any betterment.

It is evident from tables IV-VIII that there was no significant difference in various parameters after therapy among the different etiological types of heart diseases leading to CHF when the values obtained with short term treatment in the control and the study group A are compared. However,in group B that recievedcaptopril and diuretics,the average increment in urine output was greater by about 160 ml per 24 hours than in group A recieving digoxin and diuretics. A lesser increment in urine output(300 ml/24 hrs)was noted in group C.The average increment in urine output was statistically significant($p<0.001$)in all the groups.

The average reduction in heart rate was greater by about 7 beats per minute in the group recieving captopril and diuretics as compared to the control group.Reduction in heart rate was more by about 5 beats per minute in case of group C when compared with the controls.The average reduction in heart rate was statistically significant in all the 3 groups ($p<0.001$ Gp A,$p<0.01$ GpB & $p<0.025$ Gp A).

A very small increase was observed in the blood pressure in the control group while the study groups showed slight decrease in the average blood pressure.The average changes recorded in blood pressure in all the three groups wer found to be statistically insignificant.

A greater reduction was seen in JVP on an average in group C as compared to the other two groups.The average reduction in this parameter was also statistically significant ($p<0.001$)in all the three groups.The liver size also showed a greater average reduction in case of groupC.The average decrease

in liver size was also significant statistically($p<0.001$)in groups B & C,and also in the case of group A($p<0.005$).

Reduction in heart size was observed in all the 3 groups.This was comparable in groups A & B,while it was greatest in patients recieving all the 3 drugs(digoxin, diuretics and captopril),i.e.,group C.The average reduction in heart size was statistically significant in group C($p<0.05$) only.

The patients of the study groups improved their NYHA Class better as compared to the controls.The improvement in effort tolerance was appreciably striking in case of group B that did not recieve digoxin,and in which captopril was used as an alternative to this drug.

The tables IX-XIII show the effect of therapy on the various objective parameters monitored in cases of groups A,B & C during long term(more than 4 weeks)observation.The average duration of observation in follow-up was about 10 weeks.

The average increment in urine output tended to remain greatest in case of group B.The average reduction in the heart rate was again more marked in the patients recieving captopril,either along with diuretics or with both digoxin and diuretics.The decreases obtained in the average liver size and the JVP were maximum in the group recieving all the 3 drugs.It is noteworthy that 18(82%)of cases of group C had shown resistance to therapy with digoxin & diuretics.

The benefit of treatment was seen to persist in all the 3 groups in long term.In group B recieving captopril and diuretics,the objective assessment revealed persisting improvement with no attenuation of the effect of therapy.

Blood pressure was not altered significantly in any of the three groups even with long term observation.The reduction in heart size achieved was statistically significant in group C only in long term also($p<0.05$).

14(63.6%)cases of group A were showing good improvement i.e.,reduction in NYHA Class by 2 or more grades, while 7(31.8%)were showing fair(improvement by 1 NYHA Class) benefit.In group B,the improvement in NYHA Class was good for 90%(18)cases while the rest 10%(2)of the patients had improved fairly.Thus the improvement was strikingly appreciable and sustained in terms of symptomatic improvement in effort tolerance. Any deterioration was not noted in all those cases that had initially responded to treatment with captopril during long term observation.In cases of group C,16(63.6%)patients showed good improvement in NYHA Class while 5(22.7%)of the patients revealed fair improvement in NYHA Class during long term observation.

TABLE IX

Effect of therapy on various parameters in cases of the control group(group A)on long term(> 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1250 863.6±212.2	1100-1600 1370.0±142.7	+506.3
2.	Weight Kgs	32-64.8 46.6±9.4	30.6-64 44.9±9.8	-1.7
3.	Heart rate beats/mt	70-140 104.6±18.8	76-116 91.8±10.4	-12.8
4.	Blood pressure systolic mm of Hg	90-140 107.8±13.0	88-130 108.4±13.5	+0.64
5.	Blood pressure diastolic mm of Hg	40-84 70.1±13.3	30-80 68.8±9.9	-1.3
6.	JVP cms	4-11 7.0±2.3	4-10.5 4.3±1.3	-2.6
7.	Liver size	0-7 2.7±2.1	0-4.5 0.75±1.4	-1.9
8.	CT Ratio	0.44-0.76 0.56±0.03	0.43-0.71 0.53±0.07	-0.03

TABLE X

Effect of therapy on various parameters in cases of the study group B on long term(> 4 weeks) observation.

S. No.	Objective Parameter	Before therapy Range Mean ±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1200 866.5±206.9	1100-1800 1480±112.2	+613.5
2.	Weight Kgs	37.5-58 47.7±5.40	36-57 45.6±5.7	-2.0
3.	Heart rate beats/mt	96-132 104.9±11.9	76-102 84.8±8.10	-20.1
4.	Blood pressure systolic mm of Hg	100-190 127.4±26.5	100-154 121.0±15.6	-6.4
5.	Blood pressure diastolic mm of Hg	30-120 77.7±8.9	40-96 72.4±12.2	-5.3
6.	JVP cms	4-12 6.8±2.5	4-4 4±0	-2.8
7.	Liver size cms	0-8 2.9±2.3	0-6.5 0.32±0.6	-2.6
8.	CT Ratio	0.47-0.73 0.59±0.07	0.40-0.70 0.56±0.07	-0.03

TABLE XI

Effect of therapy on various parameters in cases of the study group C on long term(>4 weeks) observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1200 1006.8±121.4	900-1650 1404.7±202.3	+397.9
2.	Weight Kgs	33-72 50.2±11.3	30-68.5 48.5±10.8	-1.6
3.	Heart rate beats/mt	66-152 104.3±22.5	64-112 89.2±14.8	-17.3
4.	Blood pressure systolic mm of Hg	90-140 113.3±13.4	90-140 109.7±11.6	-3.6
5.	Blood pressure diastolic mm of Hg	30-90 71.5±15.1	30-96 69.7±10.7	-1.8
6.	JVP cms	4-15.5 9.1±2.8	4-10.5 4.5±1.7	-4.5
7.	Liver size cms	3-12.5 6.2±2.5	0-8 1.8±1.8	-4.4
8.	CT Ratio	0.46-0.80 0.63±0.09	0.43-0.74 0.59±0.08	-0.04

TABLE XII

Effect of therapy on the NYHA Class(Effort tolerance)during long term observation in the control and study groups.

NYHA Class	No.of patients Group A		No.of patients Group B		No.of patients Group C	
	I*	II*	I*	II*	I*	I
IV	9(41%)	0	9(45%)	0	13(59%)	0
III	13(59%)	2(9%)	11(55%)	0	9(41%)	1(4.5%
II	0	13(59%)	0	8(40%)	0	10(4 %
I	0	7(32%)	0	12(60%)	0	10(4 %

I*=Before therapy; II*=After therapy

TABLE XIII

Effect of therapy on the improvement achieved in NYHA Class in the control and study groups on long term(> 4 weeks)observation.

Group	Good improvement (improvement by 2 or more NYHA grades)	Fair improvement improvement by 1 NYH grade) A
A	63.6%	31.8%
B	90%	10%
C	72.72%	22%

FIG3.

MULTIPLE BAR DIAGRAM SHOWING AVERAGE INCREMENTSIN URINE OUTPUT IN THE CONTROL AND STUDY GROUPS WITH THERAPY

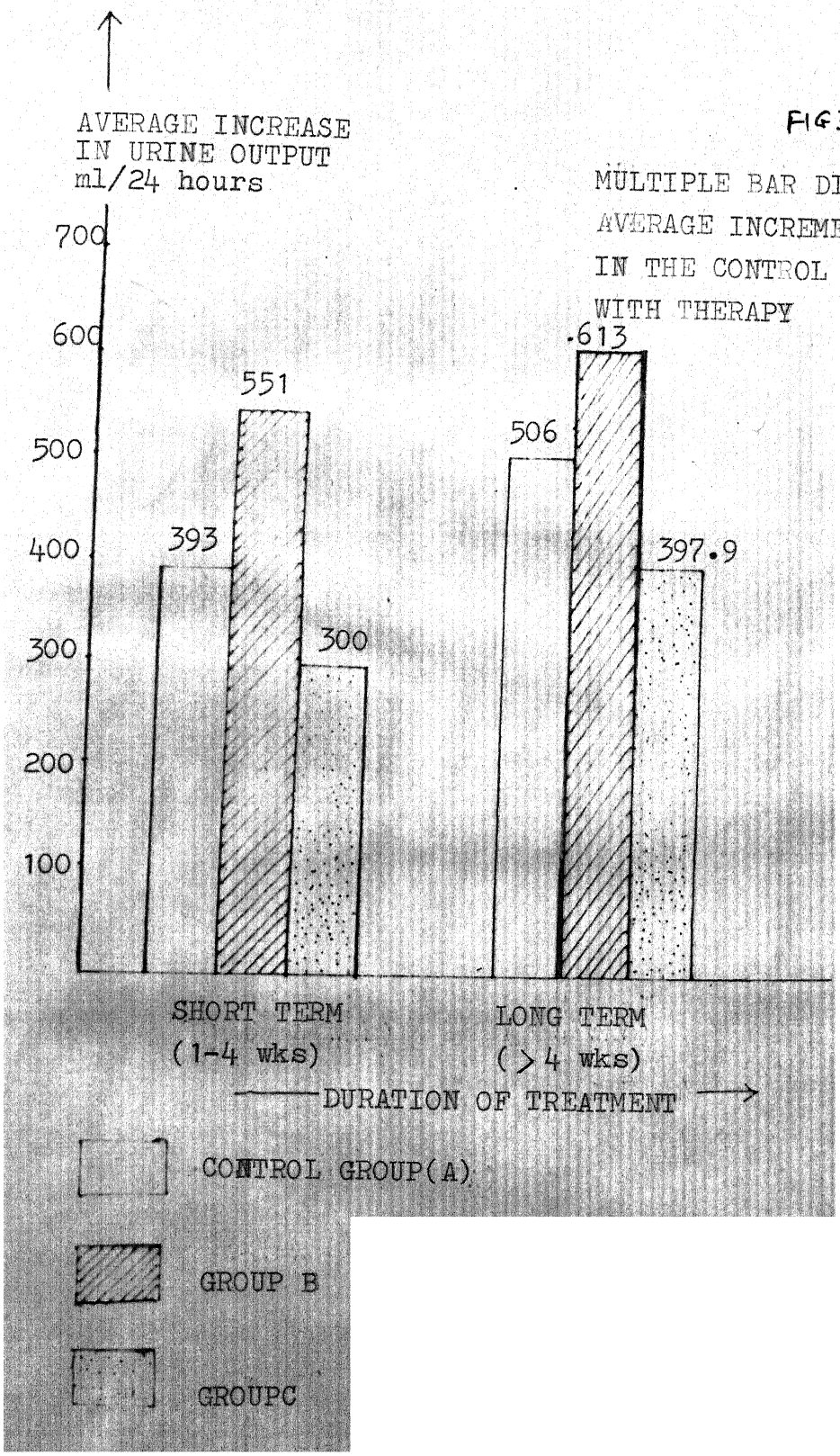
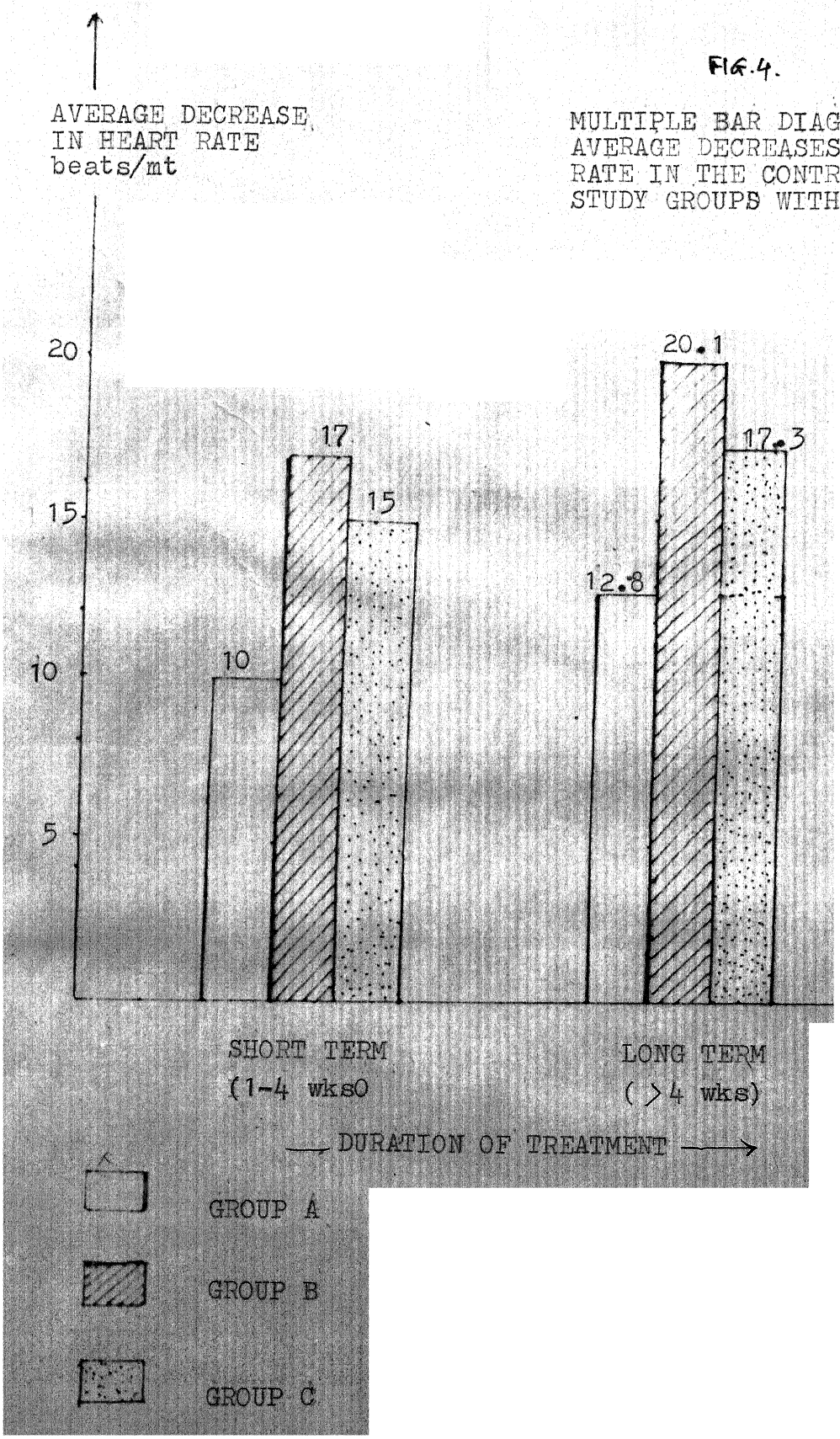


FIG.4.

MULTIPLE BAR DIAGRAM SHOWING AVERAGE DECREASES IN HEART RATE IN THE CONTROL AND STUDY GROUPS WITH THERAPY



Pg.5.

MULTIPLE BAR DIAGRAM SHOWING EFFECT OF THERAPY ON NYHA CALSS IN THE CONTROL AND STUDY GROUPS WITH THERAPY

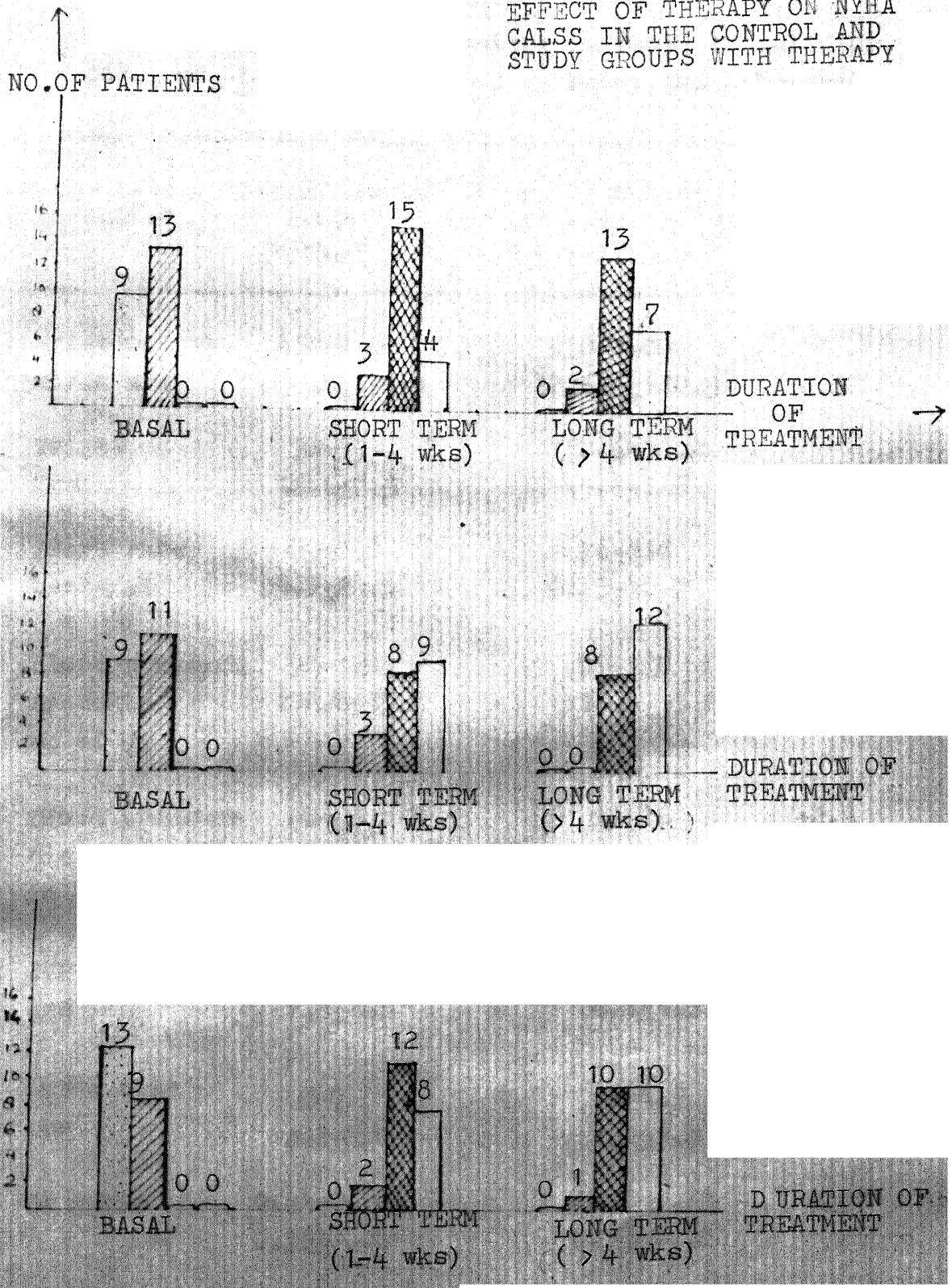


TABLE XIV

Effect of therapy on various parameters in cases of valvular heart disease of the control group(A)on short term observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1250 896.6±231.9	950-1400 1226.6±120.9	+330
2.	Weight Kgs	32-59 46.6±7.5	30.6-58.2 45.4±7.6	-1.1
3.	Heart rate beats/mt	70-140 99.7±20.5	76-116 90.5±10.7	-9.2
4.	Blood pressure systolic mm of Hg	90-140 106.6±13.7	90-150 110.4±15.9	+3.7
5.	Blood pressure diastolic mm of Hg	40-86 68±14.8	50-86 70.8±10	+2.8
6.	JVP cms	4-12 7.3±2.5	4-8.5 4.8±1.3	-2.4
7.	Liver size cms	0-7 2.8±2.0	0-4.5 1.0±1.2	-1.8
8.	CT Ratio	0.44-0.76 0.55±0.08	0.43-0.73 0.53±0.08	-0.02

TABLE XV

Effect of therapy on various parameters in cases of valvular heart disease of the control group on long term(> 4 weeks) observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1250 896.6±231.9	1100-1500 1346.6±120.9	+450
2.	Weight Kgs	32-59 46.6±7.5	29.4-59 45±8.0	-1.6
3.	Heart rate beats/mt	70-140 99.7±20.5	70-116 89.3±11	-10.4
4.	Blood pressure systolic mm of Hg	90-140 106.6±13.7	88-130 110.6±12.5	+3.9
5.	Blood pressure diastolic mm of Hg	40-86 68±14.8	30-80 68.9±11.3	+0.93
6.	JVP cms	4-12 7.3±2.5	4-10.5 4.5±1.6	-2.7
7.	Liver size cms	0-7 2.8±2.0	0-4.5 0.6±1.3	-2.2
8.	CT Ratio	0.44-0.76 0.55±0.08	0.42-0.71 0.53±0.08	-0.02

TABLE XVI

Effect of therapy on various parameters in cases of valvular heart disease in group B on short term(1 to 4 weeks)observation.

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S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	600-1200 900±214.2	1150-2000 1418±212.4	+518
2.	Weight Kgs	37.5-54 46.8±4.6	36-53 45.3±4.6	-1.4
3.	Heart rate beats/mt	88-132 104±12.7	72-100 85±7.1	-18.9
4.	Blood pressure systolic mm of Hg	100-140 117±13.2	96-130 114±9.2	-3.0
5.	Blood pressure diastolic mm of Hg	30-90 69±15.7	30-90 67.8±14.8	-1.2
6.	JVP cms	4-12 7.7±2.7	4-8 4.9±1.6	-2.8
7.	Liver size cms	0-8 3.7±2.4	0-6.5 1.5±1.8	-2.2
8.	CT Ratio	0.47-0.[illegible] 0.59±0.06	0.44-0.71 0.57±0.06	-0.02

TABLE XVII

Effect of therapy on various parameters in cases of valvular heart disease of group B on long term(> 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	600-1200 900±214.2	1200-1800 1490.9±142.7	+590.9
2.	Weight Kgs	37.5-54 46.8±4.60	36-54 44.8±4.6	-2.0
3.	Heart rate beats/mt	88-132 104±12.7	76-96 82.9±6.2	-21.1
4.	Blood pressure systolic mm of Hg	100-140 117±13.2	100-140 118.9±11.8	+1.8
5.	Blood pressure diastolic mm of Hg	30-90 69±15.7	40-86 68±12.5	-1.0
6.	JVP cms	4-12 7.7±2.7	4-4 4±0	-3.7
7.	Liver size cms	0-8 3.7±2.4	0-2.5 0.5±0.7	-3.2
8.	CT Ratio	0.47-0.73 0.59±0.06	0.44-0.70 0.56±0.06	-0.03

TABLE XVIII

Effect of therapy on various parameters in cases of valvular heart disease of group C on short term(1 to 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1200 738±202.8	900-1650 1302.3±207.8	+564.2
2.	Weight Kgs	28-73 50.5±11.4	25.5-67.8 49±10.9	-1.5
3.	Heart rate beats/mt	64-160 104.2±23	66-120 88.9±15.1	-15.3
4.	Blood pressure systolic mm of Hg	90-140 112.9±13.6	84-130 109±10.8	-3.9
5.	Blood pressure diastolic mm of Hg	30-96 70.6±14.3	40-90 69.6±10.8	-1.0
6.	JVP cms	4-15.5 9.3±2.7	4-12 5.2±2.3	-4.1
7.	Liver size cms	3-12.5 6.4±2.5	0-8 2.8±2.1	-3.5
8.	CT Ratio	0.46-0.80 0.62±0.09	0.43-0.74 0.58±0.07	-0.04

TABLE XIX

Effect of therpay on various parameters in cases of valvular heart disease of group C on long term(4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1200 738±202.8	900-1700 1397±204.6	+659.4
2.	Weight Kgs	28-73 50.5±11.4	25-68.5 49.2±10.7	-1.3
3.	Heart rate beats/mt	64-160 104.2±23	64-112 86.4±19.6	-17.8
4.	Blood pressure systolic mm of Hg	90-140 112.9±13.6	84-130 109±11.4	-3.9
5.	Blood pressure diastolic mm of Hg	30-96 70.6±14.3	40-90 69.7±10.9	-0.9
6.	JVP cms	4-15.5 9.3±2.7	4-10.5 4.5±1.7	-4.7
7.	Liver size cms	3-12.5 6.4±2.5	0-8 1.9±1.8	-4.5
8.	CT Ratio	0.46-0.80 0.62±0.09	0.47-0.74 0.58±0.08	-0.04

TABLE XX

Effect of therapy on various parameters in cases of ischemic heart disease in the control group(A)on short term(1-4 weeks) observation

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	850-950 900±40.8	900-1600 1533.3±94.2	+633.3
2.	Weight Kgs	46-64.8 56.2±7.70	44.6-64 55.2±8.0	-1.0
3.	Heart rate beats/mt	100-124 114.6±10.4	84-116 100±13.0	-14.6
4.	Blood pressure systolic mm of Hg	96-124 108.6±11.5	96-128 108±14.2	-0.6
5.	Blood pressure diastolic mm of Hg	70-70 70±0	70-76 72±2.8	+2.0
6.	JVP cms	5.5-8.0 6.6±1.0	4-4 4±0	-2.6
7.	Liver size cms	1-5 2.6±1.6	1-2.5 1.1±1.0	-1.5
8.	CT Ratio	0.53-0.61 0.56±0.03	0.50-0.57 0.53±0.03	-0.03

TABLE XXI

Effect of therapy on various parameters in cases of ischemic heart disease in the control group(A)on long term(> 4 weeks) observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	850-950 900±40.8	1500-1600 1566.6±47.1	+666.6
2.	Weight Kgs	46-64.8 56.2±7.70	44-63 54.6±7.9	-1.6
3.	Heart rate beats/mt	100-124 114.6±10.4	88-104 96±6.50	-18.6
4.	Blood pressure systolic mm of Hg	96-124 108.6±11.5	96-130 108±16.0	-0.6
5.	Blood pressure diastolic mm of Hg	70-70 70±0	66-80 72±5.8	+2.0
6.	JVP cms	5.5-8.0 6.6±1.0	4-4 4±0	-2.6
7.	Liver size cms	1-5 2.6±1.6	0-1.5 0.5±0.7	-2.1
8.	CT Ratio	0.53-0.61 0.56±0.03	0.50-0.57 0.53±0.03	-0.03

TABLE XXII

Effect of therapy on various parameters in cases of ischemic heart disease in group B on short term(1-4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	650-1000 825±125	1200-1600 1441.6±123.8	+616
2.	Weight Kgs	38-58 48±6.3	35-57.4 46.6±7.0	-1.3
3.	Heart rate beats/mt	96-126 107±10.3	78-104 89.3±9	-17.6
4.	Blood pressure systolic mm of Hg	106-150 120±17.2	106-130 111±9.5	-9.0
5.	Blood pressure diastolic mm of Hg	68-80 79±10.4	60-76 70.3±5.3	-8.6
6.	JVP cms	4-8 5.5±1.6	4-5.5 4.2±0.5	-1.3
7.	Liver size cms	0-5 2±2.0	0-1.5 0.4±0.6	-1.6
8.	CT Ratio	0.48-0.72 0.58±0.09	0.40-0.68 0.55±0.09	-0.03

TABLE XXIII

Effect of therapy on various parameters in cases of ischemic heart disease in group A on long term(> 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average
1.	Urine output ml/24 hrs	650-1000 825±125	1350-1500 1466.6±55	+641.6
2.	Weight Kgs	38-58 48±6.3	35-57 46.5±7.0	-1.5
3.	Heart rate beats/mt	96-126 107±10.3	80-102 87.3±7	-19.6
4.	Blood pressure systolic mm of Hg	106-150 120±17.2	102-136 112±11.0	-8.0
5.	Blood pressure diastolic mm of Hg	68-80 79±10.4	66-80 72±4.6	-7.0
6.	JVP cms	4-8 5.5±1.6	4-4 4±0	-1.5
7.	Liver size cms	0-5 2±2.0	0-1 0.16±0.3	-1.8
8.	CT Ratio	0.48-0.72 0.58±0.09	0.40-0.68 0.55±0.01	-0.03

TABLE XXIV

Effect on various parameters in cases of hypertensive heart failure in group B on short term(1-4 weeks) observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1100 833.3±277.8	1100-1500 1366.5±188.5	+533.3
2.	Weight Kgs	46-58 50.3±5.4	43.5-55.5 47.6±5.5	-2.6
3.	Heart rate beats/mt	96-120 104±11.3	88-100 94.6±4.9	-9.4
4.	Blood pressure systolic mm of Hg	160-190 180±14.1	140-160 148.6±8.3	-31.4
5.	Blood pressure diastolic mm of Hg	90-120 106.6±12.4	86-96 96.6±4.7	-10
6.	JVP cms	4-8.5 6±1.8	4-5.5 4.5±0.7	-2.5
7.	Liver size cms	0-3 1.8±1.3	0-1 0.66±0.4	-1.1
8.	CT Ratio	0.52-0.66 0.60±0.05	0.51-0.62 0.57±0.04	-0.03

TABLE XXV

Effect of therapy on various parameters in cases of hypertensive heart failure in group B on long term(> 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Range Mean±SD	After therapy Range Mean±SD	Average Change
1.	Urine output ml/24 hrs	450-1100 833.3±277.8	1400-1500 1466.6±47.1	+633.3
2.	Weight Kgs	46-58 50.3±5.4	43-55 47±5.6	-3.3
3.	Heart rate beats/mt	96-120 104±11.3	80-96 86.6±6.7	-17.4
4.	Blood pressure systolic mm of Hg	160-190 180±14.1	140-154 146.6±5.7	-33.4
5.	Blood pressure diastolic mm of Hg	90-120 106.6±12.4	86-96 89.3±4.7	-17.3
6.	JVP cms	4-8.5 6±1.8	4-4 4±0	-2.0
7.	Liver size cms	0-3 1.8±1.3	0-0 0±0	-1.8
8.	CT Ratio	0.52-0.66 0.60±0.05	0.51-0.60 0.57±0.04	-0.03

TABLE XXVI

Effect of therapy on various parameters in cases of congestive cardiomyopathy in group A on short term(1-4 weeks)observation.

S. No.	Objective Parameter	Before therapy Mean±SD	After therapy Mean±SD	Average Change
1.	Urine output ml/24 hrs	700±50	1175±175	+475
2.	Weight Kgs	36.8±8.8	34±10	-2.6
3.	Heart rate beats/mt	113±1.0	110±0	-3
4.	Blood pressure systolic mm of Hg	103±1.0	87±7.0	-16
5.	Blood pressure diastolic mm of Hg	81±3.0	60±0	-21
6.	JVP cms	4.7±0.7	4±0	-0.7
7.	Liver size cms	0	0	±0
8.	CT Ratio	0.59±0.07	0.57±0.07	-0.02

TABLE XXVII

Effect of therapy on various parameters in cases of congestive cardiomyopathy in group A on long term(> 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Mean±SD	After therapy Mean±SD	Average Change
1.	Urine output ml/24 hrs	700±50	1275±75	+575
2.	Weight Kgs	36.8±8.8	33.7±9.7	-3.1
3.	Heart rate beats/mt	113±1.0	103±3	-10
4.	Blood pressure systolic mm of Hg	103±1.0	91±5.0	-12
5.	Blood pressure diastolic mm of Hg	81±3.0	62±2.0	-19
6.	JVP cms	4.7±0.7	4±0	-0.7
7.	Liver size cms	0	0	±0
8.	CT Ratio	0.59±0.07	0.57±0.08	-0.02

TABLE XXVIII

Effect of therapy on various parameters in the case of congestive cardiomyopathy studied in group C during short term(1 to 4 weeks observation.

S. No.	Objective Parameter	Before therapy	After therapy	Average Change
1.	Urine output ml/24 hrs	800	1400	+600
2.	Weight Kgs	37	35.8	-1.2
3.	Heart rate beats/mt	106	96	-10
4.	Blood pressure systolic mm of Hg	120	120	±0
5.	Blood pressure diastolic mm of Hg	90	84	-6
6.	JVP cms	4.5	4.0	-0.5
7.	Liver size cms	3.5	1.0	-2.5
8.	CT Ratio	0.72	0.68	-0.04

TABLE XXIX

Effect of therapy on various parameters in the case of congestive cardiomyopathy studied in group C on long term observation.

S. No.	Objective Parameter	Before therapy	After therapy	Average Change
1.	Urine outpput ml/24 hrs	800	1500	+700
2.	Weight Kgs	37	35.4	-1.6
3.	Heart rate Beats/mt	106	100	-6
4.	Blood pressure systolic mm of Hg	120	124	+4
5.	Blood pressure diastolic mm of Hg	90	70	-20
6.	JVP cms	4.5	4	-0.5
7.	Liver size cms	3.5	0	-3.5
8.	CT Ratio	0.72	0.68	-0.04

T A B L E XXX

Effect of therapy on various parameters in cases of cor pulmonale of group A on short term(1-4 weeks)observation.

S. No.	Objective Parameter	Before therapy Mean±SD	After therapy Mean±SD	Average Change
1.	Urine output ml/24 hrs	725±175	1150±250	+425
2.	Weight Kgs	42.5±11.5	41.2±10.7	-0.25
3.	Heart rate beats/mt	118±2.0	100±0	-18
4.	Blood pressure systolic mm of Hg	119±9.0	113±7.0	-6
5.	Blood pressure diastolic mm of Hg	78±2.0	74±2.0	-4
6.	JVP cms	7.5±0.5	5.5±1.5	-2
7.	Liver size cms	4.5±1.5	2.7±0.7	-1.7
8.	CT Ratio	0.58±0.04	0.57±0.05	-0.01

TABLE XXXI

Effect of therapy on various parameters in cases of cor pulmonale of group A on long term(> 4 weeks)observation.

S. No.	Objective Parameter	Before therapy Mean±SD	After therapy Mean±SD	Average Change
1.	Urine output ml/24 hrs	725±175	1350±150	+625
2.	Weight Kgs	42.5±11.5	41.2±10.7	-0.25
3.	Heart rate beats/mt	118±2.0	93±3.0	-25
4.	Blood pressure systolic mm of Hg	119±9.0	110±10.0	-9
5.	Blood pressure diastolic mm of Hg	78±2.0	74±2.0	-4
6.	JVP cms	7.5±0.5	4±0	-3.5
7.	Liver size cms	4.5±1.5	2±1.0	-2.5
8.	CT Ratio	0.58±0.04	0.57±0.05	-0.01

SIDE EFFECTS :

Transitory asymptomatic hypotension was the most prominent or probably the only side effect seen with captopril treatment.It was observed in 4 cases(9.8%).2 of these cases were of ischemic heart disease,and 1 each of mitral stenosis and multivalvular heart disease.The hypotensive effect was seen with very low(6.25 mg) doses and persisted for 24-48 hours when the dose of the drug could be increased to produce clinical benefit.In none of the cases did it require discontinuation of the drug.In cases in whom digoxin was used premature ventricular contractions were seen to be precipitated in two, a ventricular bigemini was seen to occur in two,while three patients showed symptoms in the form of abdominal pain,vomiting and diarrhoea.

MORTALITY :

A total of 3 patients expired.Out of these 2 were cases of Aortic valve disease(kept in group A) and 1 was a cases of mitral valve disease(predominant MS,group C).The latter case expired post-operatively after undergoing mitral valve replacement.

DISCUSSION

DISCUSSION

Numerous studies exist on the use of vasodilators in CHF in the western literature.All available arteriolar & venular dilators have been tried.Sodium nitroprusside (Chatterjee et al,1973),Prazosin(Awan et al,1978),Isosorbide dinitrate(Williams DO,1977),Hydralazine(Chatterjee et al, 1976,1979),combinations of Isosorbide dinitrate(ISDN) and Hydralazine(Parmley & Chatterjee,1978),Trimazosin(Arnow & Danhey,1978),Nifedipine(Leir et al,1984),Felodipine(Temmisø et al,1984)have all been used in CHF.Among these the most successfully used was the combination of ISDN and Hydralazine. This provided both arteriolar and venular dilating properties leading to a reduction in both the afterload(by arteriolar dilation produced by hydralazine)and the preload(due to venular dilatation by ISDN).This combination was used with good results at our institution by Mishra et al in 1985-1986. The reports on the use of vasodilators in the Indian literature are relatively few.They have been tried in CHF by Ghosh et al, 1978;Khalilullah et al,1984;Bahl et al,1984 and Kaushik et al, 1984 & 1986 in their studies.In majority of these studies,the effect of vasodilators was evaluated by the use of hemodynamic parameters only.Only few of them(Joseph et al,1978;Franciosca et al,1982;Kothiala et al,1984;Conradson et al,1984)relate to clinical evaluation mainly.With research the existence of tolerance to vasodilators came to be known(Packer et al,1978; Arnold et al,1978).Gradually the role of RAS in cases of CHF was clarified.It was discovered that this system was activated in

CHF leading to adverse hemodynamic and clinical effects, studies of Levine et al, 1976; Turini et al, 1978; Davis JO, 1980; Packer et al, 1985 focus attention on this fact. It was suggested that vasodilators could also activate the RAS which might be one of the causes of tolerance to these drugs (H. Ikram et al, 1980). We thus preferred to use captopril, combining both arteriolar and venular dilating properties and mediating its effects through direct inhibition of the RAS.

The hemodynamic effects of captopril in CHF have been studied by Turini et al, 1979; Davis et al, 1979. The long term studies on the effects of captopril were conducted by Ader et al, 1980; Fouad et al, 1982; Packer et al, 1984; Cleland et al, 1984; The Captopril Multicenter Research Group, 1983 & 1985; Baylies et al, 1985. Clinical effects of therapy with captopril were assessed by Davis et al, 1979 in short term, and by Ader et al, 1980; Cowley et al, 1982; Captopril Multicenter Research Group (CMRG) 1983 & 1985; Cleland et al, 1984; Packer et al, 1984; and the Captopril Digoxin Multicenter Research Group (CDMRG), 1988, in the long term.

The effect of using captopril in cases of CHF refractory to treatment with digoxin and diuretics has been worked upon by Fouad et al, 1982; Cowley et al, 1982; CMRG 1983 & 1985 and B. Magnani, 1986. In India studies have been conducted by Mishra et al, 1986 and Kaushik et al, 1986 on these lines. The comparative effects of therapy with captopril and digoxin in mild to moderate CHF have been evaluated in the works of C. Alicandri, 1986 and the CDMRG, 1988. Studies comparing the effects

of digoxin and captopril in CHF are lacking in our country.

Our results have been compared and discussed in the light of available reports on the role of captopril in CHF as noted above. The facilities for hemodynamic assessment are lacking at our institution. It has also been realised that it is clinical improvement that matters most to the patient, for, hemodynamic improvement in absence of clinical benefit is of no value. Walsh & Greenberg, 1981; Packer et al, 1983; Kothiala et al, 1983 and Massie et al, 1984 have also corraborated that hemodynamic and echocardiographic studies are not essential in clinical practice, and in many instances, they lack correlation with the long term clinical response. Mild hemodynamic improvement may not manifest clinically, as well.

We observed the therapeautic response to therapy by monitoring objective parameters in the form of increase in urine output, changes in heart rate, blood pressure, liver size, JVP, heart size and weight; and by improvement produced in Effort tolerance.

The greatest urine output in our trial was achieved in the patients recieving captopril and diuretics, i.e., group B. The average increment in the daily urinary output also showed significant increase in cases resistant to digoxin and diuretics when they were added captopril (group C). The average increment in the urine output was about 160 ml/24 hrs greater in short term and about 110 ml/24 hrs greater in the long term in group B as compared to the control group. In

group C,the average pre-inclusion urine output was more as compared to the other groups.The reason for this was that most(82%)of these patients were already recieving optimal doses of digoxin and diuretics.The increase in urine output with addition of captopril is thus a significant observation.

The marked increases in urine output produced by captopril can be explained by the fact that captopril causes blockade of the effects of angiotensin II(thirst stimulation, vasopressin secretion and intrarenal hemodynamic changes). Captopril can bring about favourable changes in the fluid & electrolyte status by modification of pathophysiological processesss in the kidney(Lipkins & Pool Wilson,1985).Captopril enhances sodium excretion by reducing levels of plasma and urinary aldosterone(Creager et al,1981).It has also been shown to reverse the vasoconstriction in CHF and cause redistribution of regional blood flow.The natriuresis so caused may be mediated by one or more of the following:improved plasma renal blood flow,reduction in filtration fraction, suppression of hyperaldosteronism,and lowering of circulating catecholamine concentrations(Creager et al,1981).

The average decrease in the heartvrate after therapy was greater in the groups recieving captopril,either alone or in combination with digoxin.The average reduction in heart rate was about 7 beats per minute more in group B and 5 beats per minute greater in group C as compared to the controls.Kothiala et al,1983 have emphasized that this beneficial effect may be attributable to increased stroke volume.It is also indicated that myocardial oxygen demand was not increased.

Decrease in heart rate with the addition of captopril has also been noted by Ader et al,1980;Fouad et al,1982 and Kaushik et al,1986.

There was only slight decrease in the systolic and diastolic blood pressures in patients recieving captopril. Absence of significant reduction in arterial blood pressure can be explained by the rise in cardiac output with relief in CHF compensating for the fall in systemic vascular resistance. As expected in this background,there was slight increase in mean arterial pressure in the control group.

Comparable reductions in liver size and the JVP were seen in the groups A & B.The average liver size and the average JVP were greater at the time of inclusion in group C as most of the cases were of advanced CHF.However,with addition of captopril,significant improvement occurred.This is somewhat explained by the fact that 11 of these cases were having predominant MR in which good response to vasodilators can be expected.

The improvement in NYHA Class was most striking in cases recieving captopril.Therapeutic response in terms of improvement in NYHA Class was also encouraging in cases resistant to conventional decongestive therapy(group C).The improvement on effort tolerance has been observed in the studies of Ader et al,1980;Cowley et al,1982;CMRG 1983 & 1985;Cleland et al,1984;Alicandri et al,1986;B.Magnani & C.Magelli,1986;Mishra et al,1986 and the CDMRG,1988.

Majority of the patients in chronic CHF having

moderate to severe cardiomegaly may not show a decrease in CT Ratio after therapy as has been pointed out by Franciosca et al in 1980.In our study the average reduction in heart size was statistically significant in group C only.The inclusion of 1 1 cases of mitral regurgitation(MR) could account for this observation in this group.Similarly, patients having fibrotic/fatty change in the liver or those having tricuspid regurgitation(TR)may demonstrate insignificant reduction in liver size.Reduction in the JVP may not be remarkable in many patients with TR.Changes in heart rate are often very minor in cor-pulmonale.There will be a reduction in body weight and increase in urine output with the use of diuretics alone in many cases.Viewing all these facts,out of all clinical parameters NYHA Class should be taken to be of paramount importance.Changes in body weight,urine output, JVP,liver and heart size will ultimately follow the change in NYHA Class.

Overall,in our study,positive therapeautic benefit was observed in all the three groups in the short term as well as the long term.The improvement attained in the various objective parameters and the effort tolerance in cases of the control group,and the group B that recieved captopril and diuretics were comparable though the latter group showed somewhat better improvement.The majority of these cases were of mild to moderate heart failure.However,4 cases(3 with predominant MR and one with MS)were having severe CHF.These also showed good response to therapy.This is a noteworthy

feature of our study as captopril, when added to baseline diuretic therapy only has been tried in mild to moderate CHF so far. It is possible that the cases of group B might have responded to conventional decongestive therapy as well. But the equivalent or probably slightly better response obtained with the use of captopril gives stress to the fact that it could be used as an alternative to digoxin in many cases of CHF who were in sinus rhythm with predictably excellent outcome. This finding is in conformation with the studies conducted by Alicandri et al, 1986 and the CDMRG, 1988. These patients as such can be saved from the risk of exposure to the well known side effects of digoxin treatment.

The response in the groups A&B in cases of ischemic heart disease also suggests that captopril can produce marked improvement when added to baseline diuretic therapy. It has the distinct advantage over digoxin which has a tendency to cause or worsen ventricular arrhythmias while captopril has been shown to decrease ventricular ectopy (Cleland et al, 1984; Packer et al, 1984; CDMRG, 1988). The use of digoxin does not alter the afterload whose reduction can be of obvious benefit in cases of ischemic heart disease and left ventricular dysfunction. Digoxin also has the drawback of causing an increase in the myocardial oxygen demand.

Among the patients in whom captopril was used, better response was noted in cases with predominant MR, AR, IHD who recieved captopril as compared to the controls. This can be explained by improvement forward flow on reduction of

afterload.Vasodilators have been shown to be more beneficial in patients with primary cardiomyopathy,MR,IHD and post-operative low cardiac output states.On the other hand, vasodilators have been shown to be of rather doubtful value in patients having mechanical obstruction like MS & AS(Cohn & Franciosca,1977),In our study the number of cases in different etiological groups is too small to comment upon the therapeautic effect of vasodilator in relation to them.

Response to treatment with vasodilators may be difficult to evaluate in hypertensive heart failure may be ~~difficult to evaluate~~ as these cases are likely to respond even otherwise to reduction in blood pressure if brought under control by other antihypertensive drugs.However,captopril has the distinct advantage of having a potent Anti hypertensive effect. 3 cases of hypertensive heart failure studied in group B showed good improvement in objective parameters as well as the effort tolerance.Only 1 of these cases required addition of the antihypertensive methyldopa to control the blood pressure.The average dose of captopril was somewhat higher (66 mg/d)in this group(hypertensive cases).

There was no attenuation of the effects of the drug in cases who had initially shown response to captopril in short term when they were followed up in the long term. Tolerance to other vasodilators is known(Packer et al,1978; Arnold et al,1978).Activation of the RAS may be one of the possible mechanisms leading to tolerance(M.Ikram et al,1980). The captopril studies so far conducted also do not mention of

tolerance to this drug.This may be attributed to the fact that captopril is a direct inhibitor of the RAS and thus acts in a more physiological manner.

The more recent studies have employed lower doses of captopril(25-150 mg/d).The average dose of captopril used in our study was 31.25 mg per day(range 6.25-75 mg/d). Our patients were presumably of lower body weight and might not have tolerated higher doses.Short term hemodynamic improvement(Turini et al,1979;Cleland et al,1984;Bayliss et al,1985)and long term hemodynamic benefit(Ader et al,1980; Bayliss et al,1985)with low doses of captopril are well documented.Long term clinical improvement has been reported by Magnani et al,1986;Bocanelli et al,1986 and Alicandri et al,1986 with low doses of captopril.Levine et al,1980 and Sharpe et al,1980 have observed that maximal effects of captopril were evident with doses of 25 mg and a further increase in the dosage did not result in any further benefit.

The commonest side effect observed with captopril was transitory asymptomatic hypotension.It was seen in 4 cases.The hypotensive effect persisted for 24-48 hours.It was seen with even very small doses(6.25 mg/d)but waned off later when the drug could be gradually built up.The patients subsequently responded favourably to treatment.Hypotension after initial doses of captopril has been observed by Cleland et al,1984 and Packer et al,1986.Packer et al,1986 have also reported that asymptomatic hypotension does not require antidotal therapy and should not provoke discontinuation of

SUMMARY & CONCLUSIONS

SUMMARY AND CONCLUSIONS

The present study was carried out to assess the role of captopril in CHF, both as an alternative to digoxin in cases of CHF in sinus rhythm, and also as an adjuvant in cases resistant to conventional decongestive therapy (digoxin and diuretics). The period of study extended from August, 1988 to July, 1989. A total of 64 patients were studied. These were assigned to three groups-A, B & C. Group A recieved conventional decongestive therapy, group B had all patients in sinus rhythm and the cases recieved captopril and diuretics for treatment of CHF. Digoxin was witheld in these cases. Group C recieved captopril and digoxin both in addition to diuretics. Most (82%) of these cases were refractory to therapy with digoxin and diuretics. All the cases were in NYHA Class III or IV. The average dose of captopril used was 31.25 mg/day (range 6.25 mg to 75 mg/day).

The therapeautic response was evaluated by recording various parameters, viz, increase in urine output, reduction in body weight, alteration in heart rate and blood pressure, decrease in JVP, liver size and heart size (on X-Ray Chest); and symptomatic improvement in effort tolerance, according to the NYHA grading. The response was seen both in the short term (within 4 weeks) and the long term (more than 4 weeks). The average duration of follow up was 10 weeks.

Statistically significant improvements in urine

output($p < 0.001$ all groups), reduction in heart rate($p < 0.025$ group A, $p < 0.01$ group B and $p < 0.001$ group C), decreases in liver size($p < 0.005$ group A, $p < 0.001$ groups B & C), and JVP ($p < 0.001$ all groups) were observed. Blood pressure did not alter significantly in any of the groups. Reduction in heart size and of pulmonary venous congestion were observed in all the three groups, the former being statistically significant ($p < 0.05$) in group C only. Good response (improvement by 2 or more NYHA grades) was seen in 70%, 50% and 68% of groups A, B & C respectively, while, 30%, 45% and 27% of these were showing fair (improvement by 1 NYHA grade) improvement. In the long term, 63% cases of group A, 90% of group B and 72% of group C were showing good improvement in effort tolerance, while 32%, 10% and 22% of these groups respectively had improved fairly. The patients of ischemic heart disease improved better in group B as compared to the controls. Remarkable improvement could be achieved in cases of predominant MR in the groups added captopril. This led to the significant improvement seen in refractory cases of CHF, 50% of which, were having predominant MR.

In the groups recieving captopril, transitory asymptomatic hypotension was observed in 4 cases as the only side effect. A very low incidence of side effects could be due to low doses of captopril employed in this study.

4 cases of group B were having severe CHF and responded to therapy with captopril and diuretics. This was noteworthy as captopril has so far been tried in mild to

moderate CHF.

The therapeautic responses achieved in our study highlight that captopril is as,or perhaps more effective,as compared to digoxin in cases of CHF in sinus rhythm.To further evaluate its effectiveness in controlling even advanced CHF in sinus rhythm,more studies should be conducted along these lines.Significant improvement can be expected when captopril is added in cases resistant to conventional decongestive therapy.Low doses of captopril are effective in CHF and the side effects observed with these doses are relatively very few and insignificant with respect to clinical benefit it can offer.

Our observations have been compared and discussed in light of available literature on the subject.

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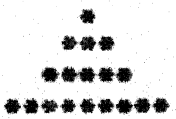

APPENDIX-1

CLINICAL STUDY OF THE COMPARATIVE EFFECTS OF CAPTOPRIL AND DIGOXIN IN CONGESTIVE HEART FAILURE

Case No. Date:

Patient's name
Age/Sex
Father's/Husband's name
Address
Religion
Ward/Bed No.
Diagnosis

PRESENTING COMPLAINTS

Breathlessness	Yes/No	Duration	Grade
Orthopnoea	Yes/No	Duration	
PND	Yes/No	Duration	
Palpitation	Yes/No	Duration	
Chest pain	Yes/No	Duration	
	Site		
	Precipitated by		
	Relieved by		
	Duration of episode		
	Frequency		
	Quality		
	Association		
Recc.respiratory infection	Yes/No	Duration	
Hemptysis	Yes/No	Duration	
Jaundice	Yes/No	Duration	
Oedema	Yes/No	Duration	
Headache	Yes/No	Duration	
Insomnia	Yes/No	Duration	
Any other			

PAST MEDICAL HISTORY(With details of drug intake)

PAST HISTORY

Rheumatic fever	Yes/No
CHF	Yes/No
	Duration
	Frequency
	Last attack
CVA	Yes/No
Any other	

FAMILY HISTORY

Diabetes	Yes/No
Hypertension	Yes/No
Heart attack	Yes/No
Stroke	Yes/No
Sudden death	Yes/No
Any other	Yes/No

GENERAL EXAMINATION

GC	Weight
Nutrition	Clubbing
Temp.	Oedema
Resp.rate	Hydration
Pallor	Nodes
Icterus	Others
Cyanosis	

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM

Dyspnoea

Orthopnoea

Pulse : Rate

Rhythm

Volume

Character

Pulsus alternans Yes/No

Peripheral pulses

Blood pressure — Upper limb
Lying
Sitting
Lower limb

Jugular venous pressure
Vertical Ht. from sternal angle
Description

Inspection
Shape of precordium
Cardiac pulsations
Apex beat

Palpation
Apex beat
Location
Character

LPH	Yes/No	Grade
Palpable S_2	Yes/No	
Thrill systolic	Yes/No	Site
Thrill diastolic	Yes/No	Site
Any other		

Auscultation
Mitral area
Heart sounds(S_1, S_2, S_3, S_4)
Murmurs(timing, character, conduction, grade, relation with respiration)

Aortic area
Heart sounds
Murmur

Acc. Aortic area
Heart sounds
Murmur

Pulmonary area

Heart sounds

Murmur

Tricuspid area

Heart sounds

Murmur

Any other

Evidences of cardiac decompensation

Dyspnoea
JVP
HJR
Liver size
Liver tenderness
Oedema
Basal crepts
Cyanosis

Evidence of SABE(IE)

Evidence of rheumatic activity

CENTRAL NERVOUS SYSTEM

EXAMINATION OF ABDOMEN

RESPIRATORY SYSTEM

INVESTIGATIONS

BLOOD :

Hb gm%

TLC cells/mm^3

DLC : P % L % E % M%

Bl.sugar(if required)- F PP R

Blood urea

Serum creatinine

Serum cholesterol (if required)

Serum Na

Serum K

SGOT(if required)

SGPT(if required)

LFT

URINE :

R/E

M/E

X-RAY CHEST PA

Cardiomegaly

Pulm.venous congestion Grade

ECG

TREATMENT GIVEN

Digoxin and diuretics

Captopril and diuretics

Digoxin,captopril and diuretics

Doses used

Duration

FOLLOW UP

Objective Parameters	Value of parameter	
	Initial	After drug therapy
Dyspnoea		
Orthopnoea		
Heart rate		
BP : Systolic		
Diastolic		
Weight		
JVP		
Liver size		
Liver tenderness		
Cyanosis		
CT Ratio		
Pulm.ven.congestion (Bettler)		
Effort tolerance (NYHA)		
24 hr urine output		
Pedal oedema		

SIDE EFFECTS SEEN DURING DRUG THERAPY

- Skin rashes
- Agranulocytosis
- Proteinuria
- Others
- Neutropenia
- Rise in serum Na
- Hypotension

SUMMARY

MASTER CHART SHOWING DIFFERENT PARAMETERS IN GROUP A

		35/f VHD	16/f VHD	16/m VHD	25/f VHD	47/m VHD	60/m VHD	40/m CorP	55/f CorP
NYHA	I*	III	III	IV	IV	III	III	III	IV
	II*	II	II	II	II	II	III	II	III
	III*	I	I	I	II	III	II	II	II
HR	I*	106	84	96	80	104	72	120	116
	II*	100	82	86	86	96	76	100	100
	III*	90	76	80	80	116	82	96	90
BP	I*	120/86	114/84	124/46	110/80	140/40	96/50	110/76	128/80
	II*	136/80	120/76	120/58	110/76	150/50	90/60	106/72	120/76
	III*	130/76	120/76	126/60	110/70	130/30	90/70	100/70	120/70
WT.	I*	58	42	38.5	46	59	54	54	31
	II*	57	41.8	37	44.4	58.2	53.5	52	30.5
	III*	57	40.4	36.6	43	59	52	52	30.5
JVP	I*	7.5	4	7.5	7.5	11	9.5	7	8
	II*	5	4	4	6.5	6	8.5	4	7
	III*	4	4	4	4	10.5	6	4	4
LS	I*	0	0	1.5	2.5	7	6	6	3
	II*	1	0	0	2	2	4.5	3.5	2
	III*	0	0	0	0	4.5	3.5	3	1
CT	I*	.52	.53	.56	.76	.55	.66	.54	.63
	II*	.50	.50	.51	.73	.52	.66	.52	.62
	III*	.50	.50	.54	.71	.53	.66	.52	.62
UO	I*	1200	1000	550	750	750	1200	900	550
	II*	1350	1300	950	1100	1200	1400	1400	900
	III*	1350	1300	1200	1400	1250	1500	1500	1200
OED	I*	-	-	-	-	+	+	+	++
	II*	-	-	-	-	-	-	±	-
	III*	-	-	-	-	-	-	-	-
BC	I*	++	++	++	++	++	+++	++	+++
	II*	+	+	±	+	++	+	+	++
	III*	+	-	-	+	+	+	+	++

I*: VALUE AT TIME OF INCLUSION IN TRIAL

II*: SHORT TERM RESPONSE (VALUE SHAWING): 1-4WKS

III*: VALUE SHAWING LONG TERM RESPONSE: >4WKS

		25/m VHD	60/f VHD	16/m VHD	15/m VHD	38/f VHD	62/f VHD	24/f VHD	16/m VHD	45/ VHD
NYHA	I*	IV	III	IV	IV	III	III	III	III	IV
	II*	II	II	II	II	II	II	I	I	II
	III*	II	II	II	II	II	II	I	I	II
HR	I*	110	70	136	90	106	116	78	108	140
	II*	86	76	116	88	96	98	76	100	96
	III*	88	80	110	86	90	96	80	96	90
BP	I*	90/80	110/80	96/60	92/50	96/80	110/78	112/76	90/56	102/80
	II*	98/70	116/76	96/70	90/60	100/86	110/76	110/76	102/64	100/70
	III*	100/76	120/70	106/70	88/70	100/76	110/80	110/70	110/70	110/70
WT.	I*	58	46	40	48	46	42	42	48	32
	II*	56.5	44.5	38.5	47	44.8	40.5	41	47	30
	III*	57	45	38	46	44.4	40.2	40.5	46.5	29
JVP	I*	4	4	6	8	4	11	7	7	12
	II*	4	4	4	4	4	4	4	4	7
	III*	4	4	4	4	4	4	4	4	4
LS	I*	0	1.5	2	2.5	1	3	3.5	4	6
	II*	0	1	0	0	0	1	0	2	2
	III*	0	0	0	0	0	0	0	0	1
CTR	I*	.45	.48	.52	.50	.56	.44	.67	.52	.56
	II*	.44	.46	.50	.50	.53	.43	.66	.50	.52
	III*	.43	.46	.50	.50	.53	.42	.66	.50	.52
UO	I*	1250	900	1000	700	1150	800	850	450	900
	II*	1350	1100	1300	1300	1300	1200	1300	1150	1100
	III*	1500	1100	1400	1200	1400	1400	1500	1500	1200
OED	I*	-	+	+	++	+	+	±	-	++
	II*	-	-	-	+	-	-	-	-	±
	III*	-	-	-	+	-	-	-	-	-
BC	I*	+++	++	++	++	++	++	++	++	++
	II*	++	-	+	+	+	+	+	+	+
	III*	±	-	+	+	+	+	±	-	±

HR:Heart rate(beats/mt);BP:Blood pressure(mm of Hg);
JVP:Jugular venous pressure(cms);LS:Liver size(cms);
CTR:Cardiothoracic ratio;UO:Urine output(ml/24 hrs);
OED:Pedal oedema;BC:Basal crepts;
-=Absent; ± = occasional; + =few;++ =moderate;+++ =gross congestion.

		55/m IHD	55/m CMP	53/m CMP	54/m IHD	53/m IHD
NYHA	I*	III	IV	III	IV	III
	II*	I	III	I	II	II
	III*	I	III	I	II	II
HR	I*	100	114	112	120	124
	II*	84	110	110	100	116
	III*	88	106	100	96	104
BP	I*	96/70	102/78	104/84	124/70	106/70
	II*	96/76	80/60	94/60	128/70	100/70
	III*	92/70	86/60	96/64	130/80	102/66
WT.	I*	58	45	45.6	46	64.8
	II*	57.2	44	44	44.6	64
	III*	57	44	43.4	44	63
JVP	I*	6.5	4	5.5	8	5.5
	II*	4	4	4	4	4
	III*	4	4	4	4	4
LS	I*	5	0	0	1	2
	II*	2.5	0	0	0	1
	III*	2.5	0	0	0	0
CTR	I*	.61	.66	.52	.53	.56
	II*	.57	.65	.49	.50	.54
	III*	.57	.65	.49	.50	.54
UO	I*	900	650	750	850	950
	II*	1600	1000	1350	1600	1400
	III*	1600	1200	1350	1600	1500
OED	I*	-	±	+	+	+
	II*	-	±	-	-	-
	III*	-	-	-	-	-
BC	I*	++	+++	+	++	++
	II*	-	++	-	-	±
	III*	-	-	-	-	-

MASTER CHART SHOWING DIFFERENT PARAMETERS IN GROUP B

		50/f VHD	32/f VHD	30/f VHD	40/f VHD	29/f VHD	25/m VHD	20/m VHD
NYHA	I*	IV	III	IV	III	III	III	III
	II*	III	II	III	I	II	II	I
	III*	II	II	II	I	I	II	I
HR	I*	96	96	108	110	88	92	9[illegible]
	II*	80	80	86	86	86	90	90
	III*	78	84	78	84	78	80	90
BP	I*	140/90	120/76	110/68	100/80	106/70	126/30	114/58
	II*	124/70	106/70	114/74	116/90	110/76	130/30	114/6[illegible]
	III*	130/70	110/70	128/76	120/86	130/80	140/40	106/58
WT.	I*	45	52	54	48	44	52	44
	II*	43	50	53	46	44	51	42.6
	III*	42.8	50.5	54	45.5	43.5	48.5	42.4
JVP	I*	8	6.5	11	6	4	7	4
	II*	4	4	6.5	4	4	4	4
	III*	4	4	4	4	4	4	4
LS	I*	1.5	3	4	3.5	0	2	1.5
	II*	0	1	2.5	1.5	0	0	0
	III*	0	0	1	0	0	0	0
CTR	I*	.51	.57	.52	.58	.47	.61	.64
	II*	.50	.56	.52	.56	.44	.60	.60
	III*	.50	.56	.50	.56	.44	.57	.60
UO	I*	700	1100	1200	850	1100	950	600
	II*	1400	1350	1500	1200	1500	1150	1450
	III*	1500	1200	1650	1400	1500	1500	1450
OED	I*	++	+	+	+	−	−	+
	II*	−	−	−	−	−	−	−
	III*	−	−	−	−	−	−	−
BC	I*	+++	++	+++	++	++	++	+
	II*	±	+	++	+	+	+	−
	III*	−	+	−	+	−	±	−

		30/f VHD	60/f VHD	30/f VHD	35/m VHD	40/f HHD	65/m HHD	21/f HHD
NYHA	I*	IV	IV	IV	IV	IV	III	III
	II*	II	II	II	II	II	I	I
	III*	I	II	II	I	II	I	I
HR	I*	132	110	120	96	96	96	120
	II*	100	88	72	78	96	88	100
	III*	96	90	76	78	80	84	96
BP	I*	112/80	140/60	120/82	100/70	160/110	190/90	190/120
	II*	104/74	120/60	120/80	96/60	146/100	140/90	160/100
	III*	106/80	118/60	120/70	100/60	140/86	146/86	154/96
WT.	I*	37.5	42.5	47	49	47	58	46
	II*	36	41	45	47	44	55.5	43.5
	III*	36	40.5	43.2	46	43	55	43
JVP	I*	12	7	8	12	8.5	4	5.5
	II*	8	4	4	8	5.5	4	4
	III*	4	4	4	4	4	4	4
LS	I*	8	6.5	4	7	3	0	2.5
	II*	6.5	2	1	2	1	0	1
	III*	2.5	1	0	1	0	0	0
CTR	I*	.73	.61	.62	.65	.66	.62	.52
	II*	.71	.60	.60	.64	.62	.60	.51
	III*	.70	.58	.60	.62	.60	.60	.51
UO	I*	800	800	600	1200	450	1100	950
	II*	1400	1350	1300	2000	1100	1500	1500
	III*	1500	1400	1500	1800	1400	1500	1500
OED	I*	-	-	++	++	+++	++	++
	II*	-	-	-	-	+	-	-
	III*	-	-	-	-	-	-	-
BC	I*	++	+	++	++	++	++	+
	II*	-	-	+	-	+	-	-
	III*	-	-	-	-	+	-	-

		63/m	63/m	65/m	49/m	45/f	50/f
		IHD	IHD	IHD	IHD	IHD	IHD
NYHA	I*	III	IV	III	III	IV	III
	II*	I	I	I	I	III	I
	III*	I	I	I	I	II	I
HR	I*	96	96	104	108	126	112
	II*	90	78	80	96	104	88
	III*	86	80	84	84	102	88
BP	I*	134/80	150/100	100/68	120/80	110/70	106/76
	II*	130/70	106/60	110/76	114/76	106/70	100/70
	III*	136/70	108/68	110/80	106/70	110/70	102/76
WT.	I*	47.5	43	52	58	45.5	38
	II*	47	41.5	50.8	57.4	48	35
	III*	47.2	41	51	57	57.8	35.0
JVP	I*	4	4	6.5	7	4	8
	II*	4	4	4	5.5	4	4
	III*	4	4	4	4	4	4
LS	I*	0	0	4.5	2.5	0	5
	II*	0	0	1.5	1	0	0
	III*	0	0	1	0	0	0
CTR	I*	.63	.48	.48	.52	.72	.65
	II*	.60	.48	.40	.50	.68	.63
	III*	.60	.47	.40	.50	.68	.63
UO	I*	800	850	700	950	1000	650
	II*	1400	1500	1200	1450	1600	1500
	III*	1500	1500	1350	1450	1500	1500
OED	I*	−	−	+	−	±	+
	II*	−	−	−	−	−	−
	III*	−	−	−	−	−	−
BC	I*	++	+++	++	+	+++	++
	II*	−	+	+	−	+++	−
	III*	−	±	+	−	+	−

MASTER CHART SHOWING DIFFERENT PARAMETERS IN GROUP C

		30/m VHD	15/f VHD	32/f VHD	40/f VHD	40/m VHD	25/f VHD	26/m VHD
NYHA	I*	IV	IV	III	IV	III	IV	IV
	II*	I	II	II	I	I	II	III
	III*	I	-	II	I	I	II	II
HR	I*	116	160	110	96	96	88	120
	II*	92	110	104	66	82	76	96
	III*	90	-	104	66	84	78	88
BP	I*	100/70	96/60	100/76	124/80	120/96	90/68	106/70
	II*	106/82	102/50	110/70	130/84	116/90	84/64	110/76
	III*	110/78	-	108/76	124/80	110/90	84/60	94/70
WT.	I*	72	38	40	58	66	52	54
	II*	67.8	37	39	56.5	64.5	50	49.5
	III*	68	-	39	56	64	50	49
JVP	I*	11	12.5	8.5	9.0	12	15.5	11.5
	II*	4	6.5	6.5	4	4	12	4
	III*	4	-	4	4	4	9	4
LS	I*	9	5.5	3.5	12.5	7.5	8.5	6.5
	II*	2.5	1	2.5	8	1	6	5
	III*	2.5	-	2	3.5	1	4	4
CTR	I*	.46	.62	.52	.55	.62	.72	.64
	II*	.43	.58	.50	.52	.60	.70	.56
	III*	.43	-	.50	.52	.60	.69	.56
UO	I*	450	450	850	600	650	500	650
	II*	1500	1350	1400	1450	900	950	1200
	III*	1500	-	1300	1600	1100	1100	1400
OED	I*	++	+	-	+	++	++	++
	II*	±	-	-	-	-	-	-
	III*	-	-	-	-	-	-	-
BC	I*	+++	+++	++	++	++	++	++
	II*	-	-	+	±	±	+	-
	III*	-	-	+	±	±	+	-

		35/f VHD	40/m VHD	35/f VHD	18/m VHD	36/f VHD	35/f VHD	55/f VHD	35/m VHD
NYHA	I*	III	III	III	IV	IV	IV	IV	III
	II*	I	II	I	II	II	II	III	II
	III*	I	II	I	I	I	II	II	II
HR	I*	84	66	88	112	104	110	64	96
	II*	82	66	80	108	96	90	72	68
	III*	80	64	84	86	92	90	68	66
BP	I*	126/86	120/60	100/58	110/30	106/60	120/70	120/70	140/90
	II*	106/70	104/56	124/80	110/40	110/60	106/66	100/68	120/76
	III*	104/70	104/56	120/76	120/40	108/64	106/66	100/70	116/76
WT.	I*	46	52	46	73	55	48	60	45.5
	II*	45	50	44.5	70	53	46	59	45.5
	III*	45	49.6	44	68.5	52	44	58	44
JVP	I*	7	9	10	11	9	12	13	4
	II*	4.5	4	4	4	7	5.5	12	4
	III*	4	4	4	4	4	4	10.5	4
LS	I*	4.5	8	6	3.5	6.5	7.5	9	5.5
	II*	3	3.5	2	2	3	2.5	8	3.5
	III*	1.5	2	1	0	1	2	8	2
CTR	I*	.70	.78	.54	.77	.61	.71	.68	.67
	II*	.66	.73	.52	.64	.57	.65	.64	.63
	III*	.66	.72	.52	.66	.57	.65	.64	.63
UO	I*	1200	650	650	800	600	750	550	700
	II*	1500	1200	1300	1200	1500	1250	900	1250
	III*	1650	1400	1600	1300	1500	1350	900	1300
OED	I*	++	++	++	-	++	++	+++	+
	II*	-	-	-	-	-	-	++	-
	III*	-	-	-	-	-	-	++	-
BC	I*	++	++	++	++	++	++	++	+
	II*	+	+	-	-	±	+	++	-
	III*	-	±	-	-	±	±	++	-

		14/f CMP	30/f VHD	55/m VHD	60/f VHD	17/m VHD	47/f VHD	10/m VHD
NYHA	I*	IV	IV	III	III	IV	IV	III
	II*	I	II	II	I	II	II	I
	III*	I	II	II	I	II	II	I
HR	I*	106	86	126	96	116	152	104
	II*	94	80	120	84	96	110	90
	III*	100	90	112	88	104	110	84
BP	I*	120/90	130/80	128/80	130/70	96/60	110/80	100/60
	II*	120/64	130/70	106/80	120/68	102/72	106/70	96/60
	III*	124/70	130/86	106/76	124 70	96/60	120/70	96/60
WT.	I*	37	48	58	44	33	54	28
	II*	35.8	45	56.4	43	31.8	52	25.5
	III*	35.4	46	55.5	42.5	31.4	52.8	25
JVP	I*	4.5	5.5	6.5	8.5	6.5	7.5	7
	II*	4	4	4	4	4	4	4
	III*	4	4	4	4	4	4	4
LS	I*	3.5	4	3.5	5	5.5	3	3.5
	II*	1	1	2.5	1.5	0	1	1
	III*	0	1	1.5	1	1	0	0
CTR	I*	.72	.62	.51	.52	.58	.53	.80
	II*	.68	.60	.50	.51	.56	.53	.74
	III*	.60	.60	.50	.50	.56	.52	.74
UO	I*	800	1100	800	900	1100	700	850
	II*	1400	1200	1650	1500	1500	1150	1500
	III*	1550	1300	1700	1600	1400	1300	1650
OED	I*	±	+	+++	++	+	+	++
	II*	–	–	–	–	–	–	±
	III*	–	–	–	–	–	–	–
BC	I*	+	+++	+++	+++	+++	+++	++
	II*	–	+	–	+	+	++	+
	III*	–	++	–	+	++	+	–